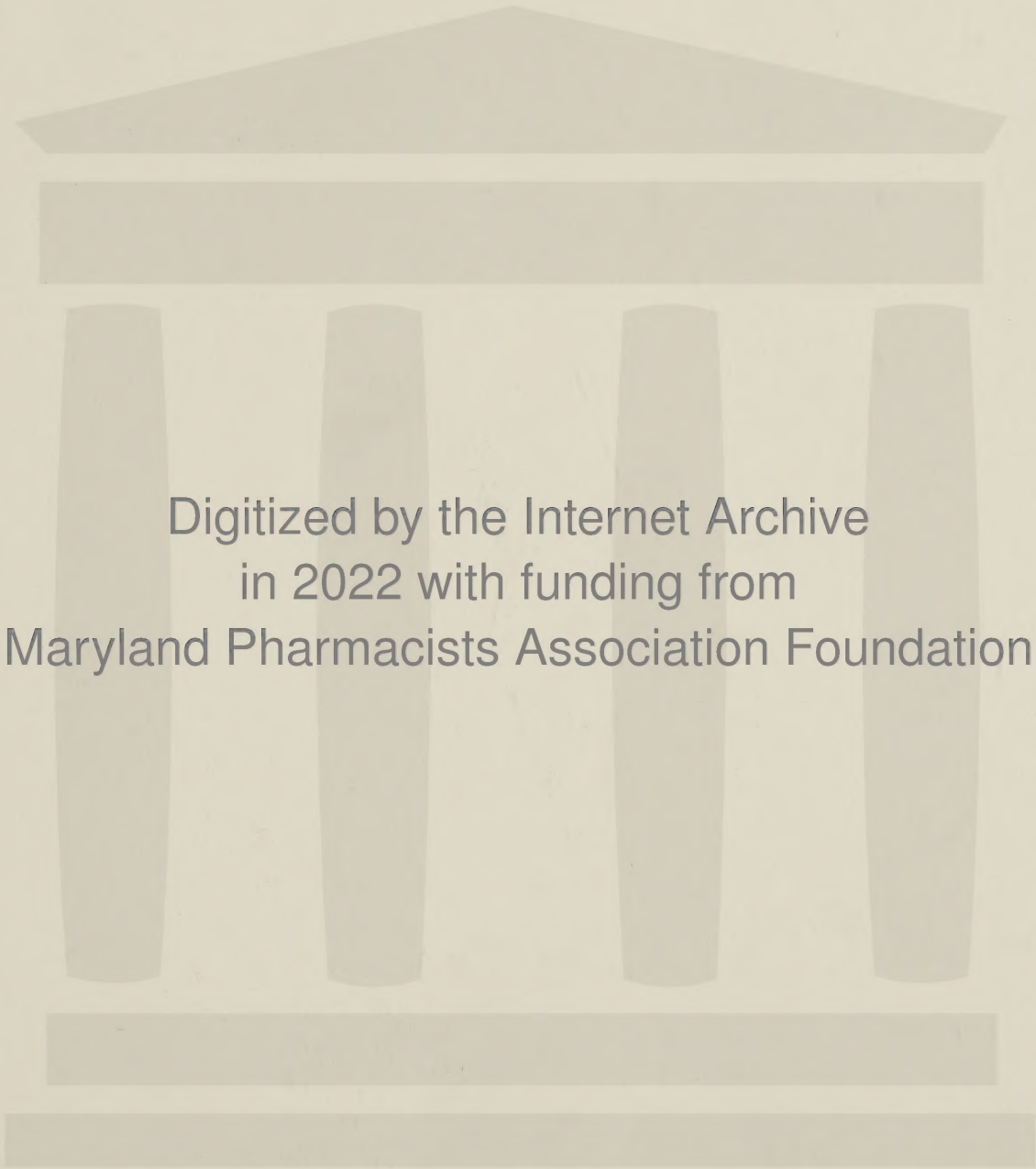


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MARYLAND
# Pharmacist
VOLUME 84 NO. 1



## MPhA'S 2008 Mid-Year Meeting

MARYLAND PHARMACISTS ASSOCIATION

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***The Official Publication of the Maryland Pharmacists Association***

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# Reflection – A 4th Year Student Pharmacist Perspective

Richard Velasco, Pharm.D. Candidate 2008

*In **Recollections, A Medical Scientist Remembers**, Dr. John C. Krantz reflects on his own experiences as a young pharmacy student in the early 1900's. The pharmacy profession as a whole has grown exponentially since that time. Despite the drastic changes that have occurred in the medical sciences one thing remains constant. The knowledge and experience that one has accumulated over time is continually passed down from mentor to student. This type of mentored learning is critical in the development of each new generation of pharmacists. Each of the professionals that I have come in contact with has contributed in some way to my development as a pharmacist. The next few paragraphs are a reflection of my own experience as a student pharmacist in my last year of school.*

I, along with many of my other classmates, began my 4th year with great relief and excitement. Relieved to know that the daily grind of classes and exams was finally over and excited to move on to the next phase of our pharmacy education. I had heard from many members of the graduating class that the 4th year of pharmacy school was a lot easier. And after 9 months of sleepless nights due to projects, exams, and presentations I was looking forward to "cruising" through 4th year. In other words, I had 3 years of pharmacy school and 4 years of undergraduate school under my belt, what more was there to learn? I figured that I would just simply show up to each of my scheduled rotations and everything would just take care of itself. And to be perfectly honest, it is entirely possible to "cruise" through rotations until they hand you that diploma in May.

When beginning my rotations I expected to be exposed to many different facets of pharmacy. I thought that I should focus mainly on things like drug information, pharmacy management, and practical pharmacy skills. Of course, I learned about all of these things, and some more. The opportunity to work with different pharmacists, in different roles, and from different backgrounds really expanded my view on the opportunities available for pharmacists. With Rick Crass at Cardinal Health I learned about how a pharmacist can play a crucial role in the development of hospital technology that improves patient care and safety. At Hill's Pharmacy with Lisa Anderson, I learned how a pharmacist can make a big difference in the local community by simply providing personal service to each of her customers. At the National Naval Medical Center, clinical pharmacists like Amy Lugo provide the health care teams on the medicine floors with invaluable expertise in drugs that not only improve patient care, but create an environment that facilitates the mutual exchange of ideas and collaboration between physicians and pharmacists. And finally, at the Maryland Pharmacists Association, long-time pharmacists like Howard Schiff continues to push for the advancement of pharmacy as a profession. The thing that impressed me the most about each of the pharmacists, of whom I have had the pleasure of working with, is their willingness to accept me as a colleague into this esteemed profession. They lead not with commands or by the display of their many accomplishments, but by the humble manner in which they carry out their daily tasks. They do not seek recognition for their actions. They seek only to satisfy that inner desire to give back to the communities in which they work, and the profession that his given them so much.

As stated earlier, it is entirely possible to "cruise" through rotations. However, by doing so, would be a great injustice not only to myself but to my mentors who have so graciously, and without expectation, taken an interest in furthering my development as a pharmacist. Through each of my different pharmacy experiences I have acquired a deep appreciation for our profession and the potential impact that it can have on the communities that we practice in. I could not help but notice that every pharmacist that I have been able to work with in the past couple of months takes great pride in the work that they do. Their eagerness to learn and share seems to be an inherent trait. I hope that I will someday be able to inspire in the same way that they have inspired me.

With only a few months until graduation I am still unsure about what I would like to do in terms of my career. There are many options, all of which have been due to the hard work and dedication of those pharmacists that have come before me. One thing that I am sure of is that as a pharmacist I will take pride and ownership of my profession. I will always remember that the title of "Doctor of Pharmacy" is not only a great accomplishment, but a promise to improve the lives around me with the knowledge and skill that I have acquired through hard work and the nurturing of my mentors.

# *Presidents' Statement*



***Joseph Marrocco, P.D.***
***President***

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As pharmacists, we are all "painted with the same brush" in many situations. I think you would agree that USA TODAY front page articles of February 12 and 13, 2008 regarding Rx errors and mistakes were unfortunate for all of us. The pharmacies involved are two of our best Rx corporations…but many of us that practice with other firms can readily identify with these scenarios.

Professor Anthony Aimed, one of my finest Duquesne professors made a comment to our class back in the 70's that rings louder, each decade…"business permeates all professions." Yes, the "bottom line" is vital to all corporate success, but when it affects our patients' safety by controlling Rx payroll expense, particularly in hours allowed regarding our pharmacy staffing-be it pharmacist, tech, or clerk- a fine line is drawn that begins to impact our patients' SAFETY and TRUST.

I challenge and urge corporate pharmacy to reexamine their focus regarding patient safety…spend your dollars wisely up front with proper staffing…as opposed to paying a lawyer for a tragic pharmacy outcome because you short staffed a pharmacy department, even after you were advised about it. Our patients entrust their family lives in us…each and every prescription is a matter of TRUST!!!

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# *"Therapeutically Speaking..."*

**Irritable Bowel Syndrome: Is the Treatment Different for Women?**

**Charmaine D. Rochester, PharmD, CDE, CDM, BCPS**
**Assistant Professor, University of Maryland School of Pharmacy**

Irritable bowel syndrome (IBS) is defined as a chronic, relapsing, but benign disorder characterized by recurrent abdominal pain, altered bowel habits, and features of disordered defecation in the absence of detectable organic disease. Within the diagnosis of IBS there are various subtypes. IBS with constipation (IBS-C) describes a patient with hard or lumpy stools for ≥25% of bowel movements; IBS with diarrhea (IBS-D) describes loose (mushy) or watery stools for ≥25% of bowel movements; mixed IBS (IBS-M) describes hard or lumpy stools for ≥25% and loose (mushy) or watery stools for ≥25% of bowel movements, while unsubtyped IBS (IBS-U) describes insufficient abnormality of stool consistency to meet criteria for IBS-C, D, or M. Women are twice as likely than men to be diagnosed with IBS, and they report a much lower quality of life than men, including problems with social relationships, work, travel, domestic activities, leisure activities and sexual intercourse, while men report difficulties with finances and work.

**Patient Case (Part 1) - History of Present Illness:** TL is a 50-year-old female who presents to the clinic with worsening bowel symptoms. She states she is usually constipated, and sometimes her stools are hard like "pellets." She describes bloating and abdominal discomfort following any large meal. TL has a history of IBS for 30 years, and iron deficiency anemia for the past six years. Her medications at this time include: dicyclomine 20 mg twice daily, amitriptyline 25 mg daily, and ferrous sulfate 325 mg three times daily.

**Clinical Presentation -** Patients with IBS typically report diarrhea with loose, mushy or watery stool, constipation with hard or lumpy stool, straining during a bowel movement, alternation between diarrhea and constipation, urgency, feeling of incomplete evacuation, passing mucus in the stool, abdominal discomfort, pain, distension, bloating, or fullness relieved by defecation. Many patients report extracolonic symptoms such as low backache, constant lethargy, nausea, thigh pain, urinary frequency, urgency or urge incontinence; dysmenorrhea or dyspareunia. Women are more likely to report symptoms of constipation, distension, mucus, nausea and psychological health problems, while men report diarrhea more commonly. Clinicians should investigate further if a patient presents with "alarm" signs or symptoms as these are indicative of organic disease and include rectal bleeding, anemia, weight loss greater than 10 pounds, late age of onset, acute onset, family history of colon cancer or inflammatory bowel disease, chronic severe diarrhea, signs of infection; and pain or diarrhea that awakens or interferes with sleep.

**Etiology and Pathophysiology** - The etiology of IBS remains unclear, but a variety of factors involved in IBS include genetics, environmental influences, previous infection, food intolerances, bacterial flora and abnormal serotonin signaling. The strongest evidence for the etiology of IBS is the role of serotonin in the GI tract. Serotonin facilitates communication between the enteric nervous system (ENS) and the central nervous system (CNS) and between the ENS and the GI tract. Impairment or imbalance in serotonergic signaling, which can affect GI motility, secretion, and visceral sensitivity, may be affected by defects or deficiencies in serotonin production or specific serotonin receptors resulting in symptoms of abdominal pain, altered bowel habits and bloating. Patients appear to have an altered gut motility as a result of food, distension, stress, and certain chemicals and an altered perception of a visceral stimuli, an altered gut reactivity and a hypersensitive gut with enhanced perception of pain. There is evidence for differences in response to treatment between women and men with IBS. There is greater efficacy of $5\text{-}HT_3$ antagonism in women with IBS-D than men. There is also a lower threshold to rectal distention postprandially, differences in GI motility, greater pain sensations, and a greater prevalence of psychological problems in women with IBS compared with men.

**Diagnosis and Goals of Therapy -** IBS has historically been a diagnosis of exclusion, although updated consensus guidelines were developed in 2006. Known as the "Rome III criteria," patients must have the following:

- "Recurrent abdominal pain or discomfort at least three days per month during the previous 3 months, which is associated with two or more of the following:
    - Relieved by defecation
    - Onset associated with a change in stool frequency
    - Onset associated with a change in stool form or appearance

- Supporting symptoms include altered stool frequency, form or passage (straining and/or urgency); mucorrhea; and abdominal bloating or subjective distention." (Ref: http://www.emedicine.com/med/topic1190.htm, accessed 1/7/08).

**Current Treatment** - Table 1 lists available agents, which include antispasmodics, bulking agents, antidiarrheals, tricyclic antidepressants (TCAs), serotonin agonists, serotonin receptor antagonists, behavioral therapy, probiotics, and acupuncture. Antispasmodic agents in the United States (US) include dicyclomine and hyoscyamine, which cause dry mouth, urinary retention, visual disturbances, and constipation. The American College of Gastroenterology (ACG) Functional GI Disorder task force suggests that there is insufficient data to make a recommendation about the effectiveness of antispasmodic agents available in the US. Bulking agents studied include wheat bran, corn fiber, calcium polycarbophil, ispaghula husk, and psyllium. These products were not effective in global IBS symptom improvement, and fiber products increase intestinal gas, bloating and abdominal discomfort. The ACG task force advises that fiber is appropriate for treatment of constipation, but may not be recommended for treatment of IBS. Loperamide is the only antidiarrheal agent appropriately evaluated for treatment of IBS, but showed no effectiveness in patients without pain or those who alternated between diarrhea and constipation (IBS-M). It improved stool frequency and consistency in IBS-M patients who had pain. The ACG Functional Disorder Task Force recommends that loperamide should not be used in IBS-C patients, and it should be used with caution in patients with IBS-M (IBS-M). Tricyclic antidepressants (TCAs) such as amitriptyline, trimipramine, desipramine, doxepin may treat the chronic pain of IBS patients. Although desipramine and doxepin showed some improvement in abdominal pain, amitriptyline was ineffective. TCA side effects include constipation, dry mouth and tiredness. The ACG Functional Disorder Task Force suggests that there is limited evidence that TCAs may decrease abdominal pain and should be used in caution in patients with IBS-C. Tegaserod is a $5HT_4$ serotonin receptor agonist, which was approved for the treatment of IBS-C. Tegaserod-using females, but not males, experienced less bloating, less abdominal discomfort and improved satisfaction with their bowel habits compared with placebo-using patients. The drug was discontinued in March 2007 when the FDA issued a public health advisory of a higher chance of heart attacks, strokes and unstable angina from tegaserod. As of July 2007 tegaserod was made available again through restricted access by a "treatment INH" for female patients with IBS-C.

Alosetron is a $5\text{-}HT_3$ receptor antagonist, which targets serotonin receptors in the GI tract. The distribution of alosetron was halted in 2000 due to concerns about ischemic colitis and serious complications of constipation, but was later FDA-approved in 2002 for restricted marketing for the treatment of women with severe IBS-D who have failed to respond to conventional IBS therapy. Trial results suggest that relaxation therapy, hypnotherapy, biofeedback, cognitive and psychotherapy may improve individual IBS symptoms for patients with co-morbid psychological disorders.

**Patient case (Part 2): Assessment** - The patient has chronic IBS-C, which is currently unstable and uncontrolled on dicyclomine and amitriptyline. Studies show dicyclomine is ineffective for the treatment of IBS. Additionally, amitriptyline, dicylomine and iron therapy could worsen her constipation.

**Plan** - Discontinue iron and re-evaluate for iron-deficiency anemia; discontinue dicyclomine and amitriptyline. The patient's symptoms should improve with the removal of these medications. She should document IBS symptoms in a symptom diary for 2 weeks and the clinician should re-evaluate therapy in 2 weeks. If no improvement with the discontinuation of these therapies, her physician could apply under the Zelnorm (tegaserod) "treatment IND," which allows restricted access to tegaserod if there is no comparable alternative drug or therapy available to treat female patients with IBS-C, and she meets the FDA approved criteria. The benefits vs. the risks should be discussed with the patient. If placed on this therapy, she should be monitored for unstable angina, heart attacks, strokes, ischemic colitis and diarrhea.

**Summary** - Although well-designed studies evaluated tegaserod and alosetron and have shown efficacy in women, neither agent is readily available for women. Both agents are available by restricted use in special circumstances. Behavioral therapy has only shown efficacy in patients with depression and anxiety. Future studies need to continue evaluating newer agents for IBS to improve the quality of life of patients, especially women. Pharmacists should educate patients on all aspects of their medication, assuring them that IBS is a benign disorder, and educating the patient about health promoting behaviors that reduce anxiety.

**Table 1: Pharmacologic Therapies for IBS**

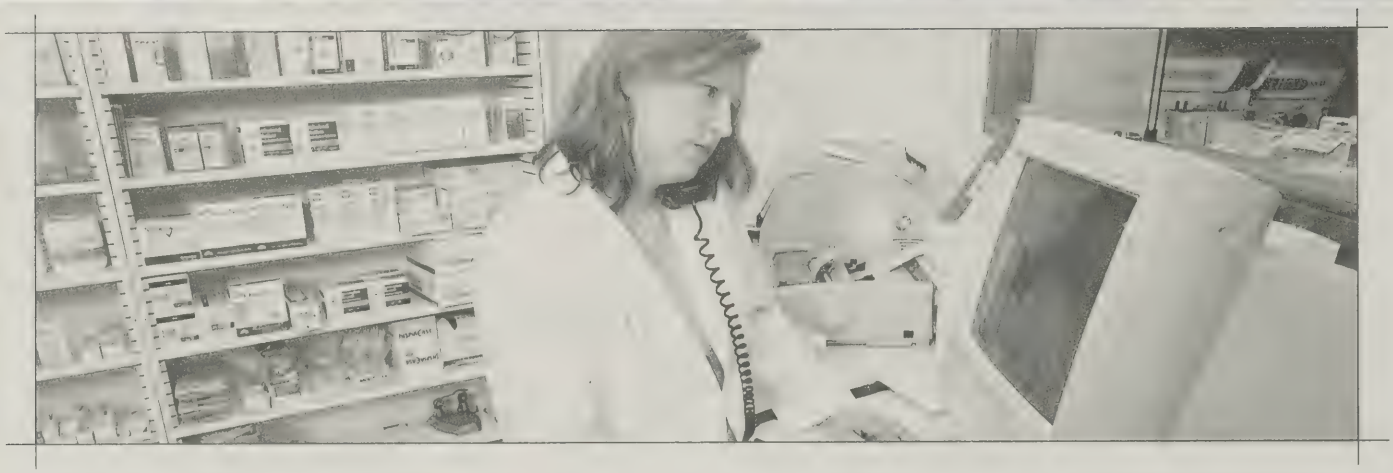
| Drug Category | Examples | Therapeutic Rationale | Primary Target Symptoms | Tolerability Concerns |
|---|---|---|---|---|
| **Traditional Therapies Target Single Symptoms** | | | | |
| Bulking agents | Wheat bran, corn fiber, calcium polycarbophil, psyllium | Accelerate intestinal transit, add fluid to stool mass, and create gel-like matrix in stool | Constipation, diarrhea | May increase intestinal gas, bloating, and abdominal discomfort |
| Osmotic laxatives | Magnesium hydroxide, sodium phosphate, lactulose, sorbitol solution | Poorly absorbed ions or sugars that cause an influx of fluid and electrolytes into the intestine | Constipation | Diarrhea, dehydration, electrolyte disorders |
| Stimulant laxatives | Senna, bisacodyl, castor oil, aloe | Reduce water and electrolyte absorption by stimulating colonic neurons and irritating the colonic mucosa | Constipation | Dehydration, electrolyte disturbances, significant cramping, and diarrhea. Should be avoided |
| Antidiarrheal agents | Loperamide | Delay intestinal transit and may enhance resting internal anal sphincter tone | Diarrhea | May cause constipation: should not be used in patients with IBS-C; use with caution in patients with alternating IBS symptoms |
| Antispasmodic agents | Hyoscyamine, dicyclomine | Anticholinergic effects and decreased spontaneous activity of intestinal smooth muscle<br><br>Decreased fluid and electrolyte secretion | Diarrhea, abdominal pain | Anticholinergic adverse effects at high doses (including urinary retention and constipation). Use with caution in patients with IBS-C |
| Antidepressants | Desipramine, amitriptyline, trimipramine, doxepin, paroxetine, fluoxetine | Decreased gut sensitivity, decreasing experience of abdominal pain<br><br>Antianxiety and antidepressant effects | Pain | Constipation, dry mouth, and dizziness are common adverse effects of TCAs<br><br>Diarrhea, nausea, nervousness, and fatigue are common adverse effects of SSRIs |
| **Multiple-Symptom Relief** | | | | |
| 5-$HT_3$ receptor antagonists | Alosetron | Reduce visceral sensitivity and colonic transit | Abdominal pain, diarrhea, urgency | Alosetron: Black box warning regarding serious consequences of constipation; ischemic colitis (reported during clinical trials and in post marketing surveillance). Only available in special circumstances. |
| 5-$HT_4$ receptor agonists | Tegaserod | Reduce visceral sensitivity and increase GI transit and intestinal secretion | Abdominal pain/discomfort, bloating, constipation | Diarrhea, ischemic colitis, unstable angina, stroke, heart attacks (reported in post marketing surveillance). Available only under restricted access. |

IBS = irritable bowel syndrome; IBS-C = IBS with constipation; TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor

References available upon request

*Edited by: Mary Lynn McPherson, Pharm.D., BCPS, Professor, University of Maryland, School of Pharmacy*

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# Pharmacy Technician Registration Process

Final Regulations for the *Pharmacy Technician Registration* were adopted January 28, 2008. Pharmacy technician candidates and pharmacy students may obtain applications from the Board's website at: www.mdbop.org/license/ tech/index.htm . Criminal Background Check forms can not be downloaded from the website. A quantity of applications and Criminal Background Check forms will be mailed to all permit holders using a staggered mailing process. Applications and forms will be mailed to candidates upon direct request to the Board.

Currently, nationally certified pharmacy technicians and grandfathered pharmacy technician candidates are the only candidates eligible to apply for pharmacy technician registration. These candidates are encouraged to register with the Board as soon as possible. Following completion of a Board-approved training program and examination*, all other pharmacy technician registration candidates may apply to the Board to become state registered.

All candidates for technician registration and students seeking exemption from registration requirements must apply to the Board before July 28, 2008 in order to continue working in a pharmacy area. If after July 28, 2008, non-pharmacist personnel working behind the counter in the pharmacy area can document that they are enrolled in Board-approved training programs, they may continue to work without registering with the Board until the training program is completed. Board approved training programs are not to exceed six months. The Code of Maryland Regulations, COMAR 10.34.34 defines the duties of the pharmacy technicians as well as the duties of the permit holders.

## *Training Program and Examination Approval Process

Training and examination programs requiring Board approval shall submit an application provided by the Board that includes the course outline, examination information, and any other information requested by the form. Go to the Board Website at mdbop.org for the application. Training programs that are preparing individuals to take a national examination approved by a board-recognized national accrediting body do not need board approval.

Pharmacy technician training programs may be offered by pharmacy employers; nationally recognized pharmacy technician training programs; accredited educational institutions' pharmacy technician programs; pharmacy technician programs approved by the Maryland State Department of Education and the Maryland Higher Education Commission; and Pharmacy technician training programs offered by the U.S. Armed Forces.

The Board will approve pharmacy technician programs offered by the U.S. Armed Forces. National pharmacy technician certification programs must have been accredited by a Board recognized national accrediting body. Currently the National Commission for Certifying Agencies (NCCA) is the only Board recognized national accrediting body. PTCB is currently the only program accredited by NCCA. PTCB can be reached at 1-202-429-7576.

Pharmacy technician training programs offered by pharmacy employers, accredited educational institutions', the Maryland State Department of Education and also programs approved by the Maryland Higher Education Commission must be approved by the Board. Board approved training programs may not be longer than 6 months and must include 160 hours of work experience. Any changes in course content shall require notification and approval from the Board. The Board may withdraw approval of a program if the Board finds that the program is in violation of regulatory requirements.

The Board will approve examinations conducted by pharmacy employers, accredited educational institutions', Maryland State Department of Education and pharmacy technician training programs approved by the Maryland Higher Education Commission if they include content criteria set forth in the Registration of Pharmacy Technician Regulations (10.34.34.01-11), contain a minimum of 100 multiple choice questions, and contain a sufficient additional questions so that the examination questions may be rotated twice a year, and a passing score of 75 percent or higher.



# Recognizing Pharmacy Excellence
# The 2008 MPhA Awards

Each year, the Maryland Pharmacists Association recognizes professional excellence through a series of awards. To nominate a pharmacist for one of the awards described below, complete the Official Award Nomination Form. The forms should be submitted to: Award Nominations, c/o Maryland Pharmacists Association, 650 West Lombard Street, Baltimore, Maryland 21201-1572.

All nominations will be reviewed by the Past Presidents Council who is responsible for selecting the award recipients. The decision of the Council is final. Award recipients will be notified in advance of the award's presentation at the Annual MPhA Convention.

For consideration, all nominations must be received no later than ***Friday, April 4, 2008.***

- **Pharmacists Mutual Distinguished Young Pharmacist Award**
  Awarded to a pharmacist who graduated within the past ten years and has made a significant contribution to the profession through service to a local, state or national pharmacy organization. ***Who is Eligible:*** Any MPhA pharmacist member who graduated from pharmacy school in 1998 or after.

- **Maryland Pharmacists Association Honorary President**
  An honorary position on the Board of Trustees given to a person, not necessarily a pharmacist, who has worked for the MPhA or Maryland Pharmacy over a long period of time. ***Who is Eligible:*** Any long standing contributor to the profession or the Association.

- **MPhA Mentor Award**
  This award recognizes individuals who encourage pharmacists, technicians, and/or student pharmacists in the pursuit of excellence in education, pharmacy practice, service, and/or advocacy. ***Who is Eligible:*** Any MPhA pharmacist member who meets the criteria of the Award.

- **Seidman Distinguished Achievement Award**
  Created to honor the major impact on the pharmacy profession by Henry Seidman, this award is presented for outstanding service by a Maryland pharmacist to the pharmacy profession during *either* the past year or over a period of years. ***Who is Eligible:*** Any MPhA pharmacist member who meets the criteria of the award.

- **Wyeth-Ayerst Bowl of Hygeia Award**
  The Bowl of Hygeia recognizes a pharmacist who has performed outstanding services to the community in any area, with a particular emphasis on non-pharmacy contributions. ***Who is Eligible:*** Any MPhA member pharmacist who has not already received the Bowl of Hygeia.

- **Innovative Practice Award**
  Established in 1993, this award aims to recognize forward-thinking pharmacists who have expanded their practices into new areas. Any practicing pharmacist member within the geographic area who has demonstrated innovative pharmacy practice resulting in improved patient care. ***Who is Eligible:*** Any MPhA pharmacist member who meets the criteria of the award.

# Maryland Pharmacists Association
# Award Nomination Form

To nominate a Maryland pharmacist for one of MPhA's annual "Recognizing Pharmacy Excellence" awards, this form must be completed and returned to the Maryland Pharmacists Association no later than ***Friday, April 4 , 2008***. All nominations will be held in strictest confidence by the MPhA Past Presidents Council, which is responsible for selecting the award recipients. The decision of the Council is final. Award recipients will be notified in advance of the presentation of the award.

Please consider the following nominee for:

☐ ***Pharmacist Mutual Distinguished Young Pharmacist Award***
Nominee _____
Address _____
City, State & Zip _____
Daytime Phone _____
Employment/Practice _____
Nominated by _____ Nominator's Phone _____

☐ ***Seidman Distinguished Achievement Award***
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Attach a current resume or curriculum vitae for the nominee that shows their professional and personal achievements. This information is essential for the Past Presidents Council to make its decisions as to which candidates will be recipients of the "Recognizing Pharmacy Excellence" awards. In addition, the nominator should attach a brief letter explaining why the nominee is worthy of receiving this award.

Return the completed form to:

**Awards Nominations**
c/o Maryland Pharmacists Association
650 W. Lombard Street
Baltimore, MD 21201-1572

Fold

**2008 Awards Nominations**
Maryland Pharmacists Association
650 W. Lombard Street
Baltimore, MD 21201-1572

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# Continuing Education for Pharmacists

Volume XXIV, No. 11

## Cervical Cancer: Prevention by Immunization Against Human Papillomavirus Infections

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**Goals.** The goals of this lesson are to discuss the association between human papillomavirus infection and cervical cancer, and describe the new vaccine to prevent HPV infection.

**Objectives.** At the conclusion of this lesson, successful participants should be able to:

1. summarize key points relative to the human papillomavirus (HPV);
2. identify the pathological response to infection by HPV;
3. describe the new vaccine for prevention of HPV infections in terms of its physiological and clinical characteristics; and
4. select from a list important points to convey to patients relative to the new vaccine.



Gossel



Wuest

### Introduction

About 1400 women worldwide are diagnosed with cervical cancer every day, resulting in more than 500,000 new cases and 276,000 deaths annually. More than 10,000 new cases of cervical cancer will be diagnosed and 4000 deaths recorded in the U.S. in 2006. Human papillomaviruses (HPVs) are the primary cause of cervical cancer. In fact, of the 10 million cases of all types of cancer that develop annually throughout the world, more than 15 percent are estimated to be attributed to infectious agents. Infection by HPVs accounts for approximately 30 percent of virus-induced cancers.

### Etiology and Pathogenesis

***HPV Infection***. HPV infection is believed to be the most common sexually transmitted infection in the U.S. and worldwide. The HPVs include a group of approximately 120 small DNA viruses, of which about 40 can infect the epithelial lining of the genital tract. Of the approximate 40 types, HPV 16 and HPV 18 are considered high-risk oncogenic types, and account for development of about 70 percent of all cervical cancer cases. In addition to cervical cancer caused by HPV types 16 and 18, infection with low-risk HPV types such as 6 and 11 can result in anogenital warts (condyloma acuminata), which are outgrowths of the cervicovaginal or vulvar tissues and external genitalia. They rarely cause cancer. The HPVs also cause other, less common, types of cancer (Table 1). Among them are vulvar and vaginal cancer in women and penile cancer in men.

Epidemiological evidence linking cervical cancer with HPVs was confirmed in the 1980s when HPV DNA was identified in virtually all cervical cancer cells and precursors. It is now accepted that HPV infection is necessary for development of virtually all cervical squamous cell carcinomas and adenocarcinomas. HPV infection is usually transmitted during sexual intercourse. The risk of infection within five to seven years of the first sexual contact is 50 percent, with a 70 percent lifetime risk. One study of more than 600 female university students revealed that 24 months after sexual activity, the incidence of HPV infection was 40 percent. Most HPV infections are transient (i.e., benign), however, and only 3 to10 percent of women will become persistent HPV carriers and constitute the high-risk group who will contract cervical cancer.

Condoms offer limited protection against HPV transmission. Perinatal infection may occur via maternal transmission, through amniotic fluid during gestation or delivery, or direct exposure to HPV lesions of the cervix or genitalia during birth, thus resulting in laryngeal papillomatosis. This rare, but debilitating, disease results in papillomas (benign tumors derived from epithelium) that obstruct the airway. Postnatal transmission by non-

**Table 1**
**Cancer types attributed to HPV Infection**

| Cancer Type | Association With Certain HPV Types (%) |
|---|---|
| Cervical* | ≥95 |
| Vaginal* | 50 |
| Vulvar* | >50 |
| Penile | 50 |
| Anal | >70 |
| Oropharyngeal | 20 |
| Nonmelanoma skin/cutaneous | 90† |

*Includes cancer and intraepithelial neoplasias
†Immunocompromised patients
Adapted from Pichichero ME. *Clin Pediatr* 2006;45:393.

sexual activities has also been documented.

***Risk Factors***. Young age (20 to 24 years for females; 25 to 29 years for males) is the most significant risk factor for development of HPV infection. Most risk factors (Table 2) are linked to sexual behavior, including the total number of sexual contacts. Women who are HPV-positive for type 2 herpes simplex virus (HSV-2) or *Chlamydia trachomatis* antibodies are at moderately increased risk. Males who are not circumcised are at increased risk of acquiring HPV infection or transmitting it to a sexual partner of either gender. Having sexual intercourse at an early age is a risk factor for females, as well as having intercourse with sexually promiscuous male partner(s). HPV-positive women who report seven or more full-term pregnancies have a four-fold increased risk of cervical cancer as compared to similar HPV-positive women who are nulliparous (have never given birth). Smoking is associated with a two-fold statistically significant increased risk of cervical cancer. Among HPV-positive women, any use of oral contraceptives is associated with an increased risk of cervical cancer.

***Cervical Cancer.*** In women worldwide, cervical cancer is second to breast cancer as the most common cancer, and generally the most common cause of death from cancer. It is the eleventh most common cancer among women in the United States. In developing countries, cervical cancer is the most frequent cancer in women, with more than 80 percent of new cases appearing in these locales.

**Prognosis of Human Papillomavirus Infection**

Seventy to 90 percent of HPV infections are transient in women at high risk for HPV infection. The median duration of new HPV infection shown in a longitudinal study of female university students was eight months. Infection is considered persistent when the same HPV type can be detected two or more times in the same woman within several months to a year. Factors correlated with persistent HPV infection include older age, high risk types of HPV (i.e., HPV 16 and/or 18), infection with multiple types of HPV, and immune suppression. Consecutive premalignant stages (i.e., cervical intraepithelial neoplasias [CIN]) are involved in progression from persistent infection with HPV to cervical cancer, usually over a period of 12 to 15 years.

***Cervical Screening***. Cancer of the cervix is unique among malignant diseases. It has a well-characterized and long-lasting pre-invasive phase which invariably precedes clinical cancer. Cervical cancer prevention, therefore, focuses on routine screening with the Papanicolaou test (Pap smear) followed by early intervention. The Papanicolaou test aids detection of early dysplastic (abnormal tissue growth) and neoplastic cellular changes, thereby reducing cancer-associated mortality by more than two thirds. Countries with organized cervical cancer screening programs report a marked reduction (in compliant individuals) of nearly 75 percent in the incidence of invasive cancer.

Cervical screening imposes technical limitations and results are sometimes difficult to interpret. Moreover, screening and treatment are not equally accessible to all groups of women; more than half of all cervical cancer cases in the United States occur in women who have never or rarely been screened. Although the Papanicolaou test is significant from its historical perspective, its impact on the incidence of cervical cancer, and its position as the most widely used cancer screening test in the world, must be realistically considered. Recent publications suggest that the sensitivity of the Pap smear is only 50 to 60 percent.

Cost-effective public health strategies designed to reduce the risk of cervical cancer in vulnerable groups are a high priority. From a national policy perspective, among the most pressing concerns are the escalating costs associated with current screening practices. For example, more than $6 billion is spent each year in the United States on the evaluation and management of low-grade lesions, the majority of which would regress naturally without intervention. At present, these lesions cannot be identified as such. The need for a vaccine to prevent HPV infection, and thus cervical and other less common cancers, is therefore apparent.

**Quadrivalent HPV (Types 6, 11, 16, 18) Recombinant Vaccine**

A non-infectious recombinant, quadrivalent vaccine (Gardasil/ Merck & Co., Inc.) has been approved for use in the United States. It is prepared from the highly purified virus-like particles (VLPs) of the major capsid protein of HPV

Types 6, 11, 16, and 18. Vaccine proteins are produced by separate fermentations in recombinant *Saccharomyces cerevisiae*, and assembled into VLPs. VLPs are morphologically and antigenically similar to natural virions and, consequently, induce a potent neutralizing immune response following vaccination. They do not contain the viral genome and, therefore, cannot spread infection.

Efficacy was assessed in an early clinical trial involving 552 young women (age 16 to 23 years) who received the vaccine or placebo. The primary end point was the combined incidence of infection with one or more of the oncogenic (cancer causing) HPV types, or cervical or external genital disease (i.e., persistent HPV infection, HPV detection at the last recorded visit, CIN, cervical cancer, or external genital lesions caused by one of the HPV types in the vaccine). Vaccine efficacy was 100 percent for prevention of clinical disease associated with the HPV types. Overall, the combined incidence of persistent infection or disease with HPV types 6, 11, 16, or 18 declined by 90 percent in women who received the vaccine compared with those given placebo. The study was not powered to assess vaccine efficacy for specific disease end points. Only six women (all in the placebo group) developed genital warts or type-specific CIN during follow-up. The vaccine proved to be highly immunogenic, with all patients showing evidence of HPV 6-, 11-, 16- and 18-specific antibodies following vaccination. There were no serious vaccine-related adverse events.

A more recent study enrolled 12,167 women aged 16 to 26 years at 90 centers in 13 countries. The study was double-blinded; women were randomized to receive three doses of the quadrivalent vaccine or placebo over six months. Recipients of a full course of vaccine who were free of infection with HPV types 16 and 18 at month 7, were 100% infection free at 17 months. In the 5301 vaccinated women, there were no observed cases of high grade precancers or non-invasive cancer (CIN 2 or 3 or adenocarcinoma) related to HPV 16 or 18. There were 21 cases in the women who received placebo.

***Mechanism of Action***. HPV is specific for humans, but animal studies with papillomaviruses suggest that the efficacy of the VLP vaccines is attained through development of immune responses. Gardasil prevents HPV 6-, 11-, 16-, and 18-related cervical cancer, cervical dysplasias, vulvar or vaginal dysplasias, or genital warts from occurring.

**Adverse Effects**. In premarketing clinical trials, vaccine-related adverse experiences included pain, swelling, redness, itching, and fever.

Gardasil may be given concomitantly with hepatitis B vaccine (recombinant) but at a separate injection site. Co-administration with other vaccines has not been studied.

Subjects in premarketing clinical trials who used hormonal contraceptives did not experience an altered response to the vaccine. Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and high doses of corticosteroids, may interfere with the immune response to vaccines.

Hypersensitivity to the active substances or to any excipients in the vaccine is a contraindication to its use. Individuals who develop symptoms suggestive of hypersensitivity after receiving a dose of Gardasil should not receive further doses.

***Indications and Uses***. Gardasil is indicated for prevention of the following diseases caused by HPV types 6, 11, 16, and 18 in girls and women nine to 26 years of age:

- Cervical cancer
- Genital warts (condyloma acuminata) and the following precancerous or dysplastic lesions:
- Cervical adenocarcinoma *in situ*

**Table 2**
**Risk Factors for Human Papillomavirus Infection**

**Females**
Young age (peak age group, 20 to 24 years)
Lifetime number of sexual partners
First sexual intercourse at early age
Male partner's overall sexual behavior
Smoking
Oral contraceptive use
Previous pregnancies
Uncircumcised male partners

**Males**
Young age (peak age group, 25 to 29 years)
Lifetime number of sexual partners
Lack of circumcision

Adapted from: Pichichero ME. *Clin Pediatr* 2006;45:393.

- Cervical intraepithelial neoplasias grade 2 and grade 3
- Vulvar intraepithelial neoplasias grade 2 and grade 3
- Vaginal intraepithelial neoplasias grade 2 and grade 3
- Cervical intraepithelial neoplasias grade 1

The vaccine does not protect against infection by HPV types not contained in the vaccine or diseases that are not caused by HPV. Individuals with impaired immune responsiveness, whether due to use of immunosuppressive therapy, a genetic defect, HIV infection, or other causes, may have reduced antibody response to active immunization. Safety and efficacy have not been assessed in girls younger than nine years or women older than 26 years.

As is true with other intramuscular injections, Gardasil should not be given to individuals with bleeding disorders, including hemophilia or thrombocytopenia, or to individuals using anticoagulant therapy, unless the potential benefits from the vaccine clearly outweigh the risk of administration. If the decision is made to administer Gardasil to such persons, it should be given cau-

tiously with measures to avoid the risk of hematomas.

***Dosage, Administration, and Availability***. Gardasil is given intramuscularly as three separate doses: first dose at a chosen date, second dose two months after the first dose, and third dose six months after the first dose. Injections should be administered in the deltoid region of the upper arm or in the higher anterolateral area of the thigh. The vaccine should not be injected via any other site.

Gardasil is available in prefilled syringes and vials for single use. The vaccine should be stored under refrigeration, brought to room temperature, and shaken well before use. No dilution or reconstitution of contents is necessary.

***Patient Information***. Information to convey to the patient, parent, or guardian includes the following points:

- Vaccination does not substitute for routine cervical cancer screening. Women who receive Gardasil should continue to undergo cervical cancer screening.
- Be sure to read the information that is provided with each vaccination.
- Report any adverse reaction to the vaccination to your physician.
- Do not receive the vaccine if pregnant.
- This vaccine is maximally effective following three injections spread over six months. Be sure to complete the immunization series, unless contraindicated.

**Anticipated Impact of HPV Vaccination in the United States**

It is difficult at present to predict the impact of the new vaccine on HPV infection and cervical and other cancers caused by HPV. However, it is possible to arrive at some estimates. The greatest short-term impact in developed nations such as the United States will be a reduction in the overall number of CIN 2 or 3 cases to about one-third to one-half as many such lesions in vaccinated women compared with non-vaccinated women, given that, as noted earlier, HPV 16 and HPV 18 together account for approximately 70 percent of such lesions. This level of protection can translate to a substantial reduction in morbidity and treatment together with a reduction in related costs. The eventual reduction in the incidence of cervical cancer and its consequences can be anticipated to be at least as great. If the vaccine were widely administered to populations that historically are less likely to be screened regularly, it could prevent most serious infections that currently are not detected. The impact on subclinical and low-grade dysplasias would be expected to be more modest, since only a minority of these infections are attributable to HPV types 6, 11, 16, or 18. Although these anticipated reductions in CIN 2 or 3 and invasive cervical cancer are impressive, it must be recalled that there would still be many serious HPV infections against which the vaccine will not protect. Therefore, it will still be necessary for vaccinated women to follow the most current cervical cancer screening guidelines.

Another HPV vaccine for use in women is also in development, but was not yet available at the time this lesson was prepared. GlaxoSmithKline is testing a bivalent vaccine against HPV types 16 and 18 that is also administered in three doses (at birth, one month, and six months).

**Vaccine Use in Males**

Although the immune response of men to the approved vaccine seems to be similar to that of women, it is not known whether the vaccine will confer protection in men or reduce their ability to transmit HPV to others. Gardasil is not approved for use in men.

While many vaccines have comparable efficacy in males and females, a subunit vaccine for herpes simplex virus (HSV-2), another sexually transmitted viral infection, was shown to be effective in women but not in men. This raises the possibility that an analogous difference might be noted with the HPV vaccine. HSV-2 infection is more likely to be mucosal in women and cutaneous in men; therefore, the difference in protection from the HSV vaccine might be attributable to higher antibody titers in mucosa than in skin. At the same time, the high level of protection afforded by the new vaccine against cutaneous genital warts in women would also be expected to apply to men, since these warts appear on keratinized skin in both genders. Future efficacy trials of the HPV vaccine in men will most likely address this issue.

**Overview and Conclusion**

The thought that cervical cancer and other cancer types caused by HPV can be safely and effectively prevented by a vaccine is both exciting and challenging. Candidates for the new quadrivalent HPV vaccine now have a means of protection against HPV infection caused by four common HPV types. HPV vaccination will most likely result in health gains that will justify the cost.

# Continuing Education Quiz

This month's questions are taken from the article on "Cervical Cancer: Prevention by Immunization Against Human Papillomavirus Infections". Circle your answers to the following questions and mail the entire page to Maryland Pharmacist CE, 650 W. Lombard Street, Baltimore, MD 21201-1572. There is no charge for this quiz for MPhA members (non-members $ 10.00). The completed quiz for this issue must be received by 11/15/09. A continuing education certificate for one and one-half contact hours (0.15 CEUs) will be mailed to you within six to eight weeks. Please type or print clearly. ACPE# 129-144-06-011-H01.

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1. The types of HPV infection that most likely result in cervical cancer are:
   a. 6 and 11.
   b. 6 and 16.
   c. 11 and 18.
   d. 16 and 18.

2. All of the following statements are true EXCEPT:
   a. HPV infection is necessary for development of virtually all cervical squamous cell carcinomas.
   b. if used correctly, condoms offer nearly complete protection against HPV transmission.
   c. HPV infection is usually transmitted during sexual intercourse.
   d. most HPV infections are transient and benign.

3. All of the following are linked to an increased risk of cervical cancer EXCEPT:
   a. previous pregnancies.
   b. smoking in females.
   c. use of oral contraceptives.
   d. circumcision in males.

4. Countries with organized cervical cancer screening programs report a reduction (in compliant individuals) in the incidence of invasive cancer of nearly:
   a. 25 percent.
   b. 50 percent.
   c. 75 percent.
   d. 100 percent.

5. Gardasil is a:
   a. quadrivalent vaccine.
   b. trivalent vaccine.
   c. bivalent vaccine.
   d. monovalent vaccine.

6. Gardasil may be given concomitantly with which of the following vaccines?
   a. Herpes Simplex
   b. Hepatitis A
   c. Herpes Zoster
   d. Hepatitis B

7. Gardasil is indicated for use in females:
   a. 6 to 18 years of age.
   b. 9 to 26 years of age.
   c. 13 to 35 years of age.
   d. 20 to 40 years of age.

8. Which of the following is true?
   a. Vaccination does not substitute for routine cervical cancer screening.
   b. Females who receive Gardasil do not need to undergo cervical cancer screening.

9. Gardasil is maximally effective following:
   a. a single injection.
   b. two injections spread over three months.
   c. three injections spread over six months.
   d. four injections spread over 12 months.

10. All of the following are true about Gardasil EXCEPT:
   a. it is approved for use in males.
   b. it is stored under refrigeration.
   c. dilution or reconstitution is not necessary.
   d. it is administered in the deltoid region of the upper arm.



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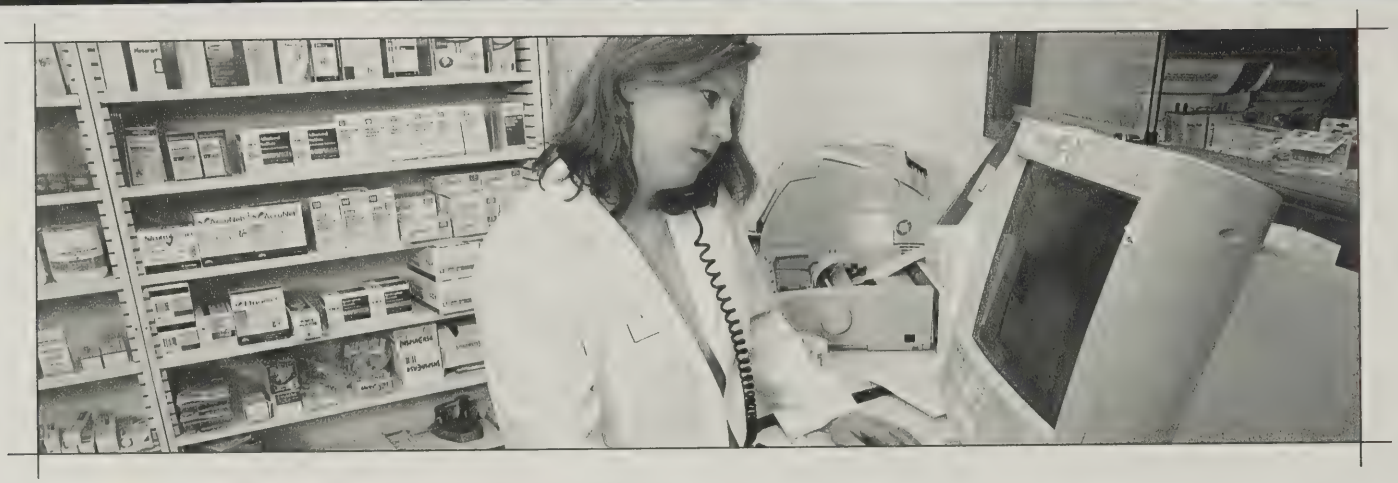

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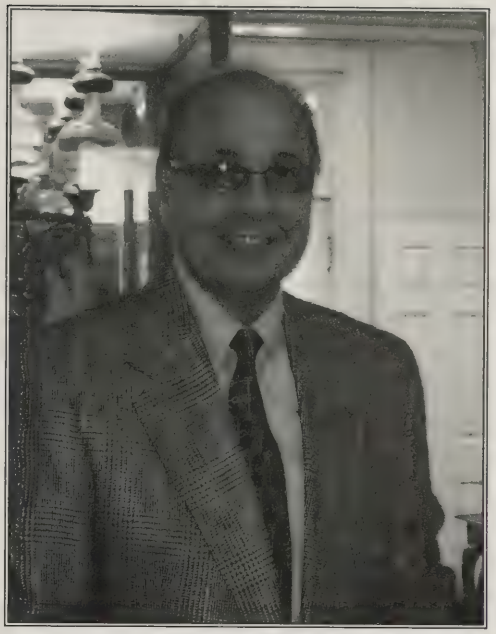
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# *Presidents' Statement*



***Joseph Marrocco, P.D.***
***President***

***To my valued colleagues of MPhA, it has been a privilege and honor to serve as your President this past year.***

As I conveyed to you last summer at installation, our MPhA Board of Trustees strived to represent our membership, and our Pharmacy profession at the highest level possible, ultimately with our patients best interest and outcomes in mind.

Perfect and near perfect attendances were realized at our monthly Trustee meetings. Fellow members like yourselves, attended our meetings, and their opinions and points of interests and concerns were discussed as new business.

I applaud the attendance and participation of our University of Maryland School of Pharmacy on many levels, from Dean Natalie Eddington to ASP (the APhA student chapter) President, Claire Leocha and President-elect Kim Wu. Members' phenomenal involvement, professional demeanor, and genuine compassion, on Maryland Legislative Day, Feb 14, 2007 at the Annapolis General Assembly exhibited a powerful voice and signal to our state legislature that our patients are our utmost concern. In all facets of our practice YOU commanded the state legislature's "eyes and ears".

Our MPhA Board of Committee Chairs devoted many hours and efforts to promulgate our profession in the highest manner possible, always striving to "look down the road". The ability to think "out of the box" was highly evident during our meetings and their undertakings.

I commend Executive Director, Howard Schiff, Office Manager, Elsie Prince, Chairperson Ginger Apyar and Past Chair, Matt Shimoda. Their wisdom and insights on behalf of MPhA were noble.

I salute the following Chairs, along with their committee members, for their stellar undertakings:

Communications—Michelle Andoll; Legislation—Brian Hose; Meetings—Doris Voigt; Budget—Walter Abel; Building and Property—Doug Campbell; Nominating—Magaly Rodriguez de Bittner; P3 Program—Christine Lee; Membership—Mary Kremzner; Professional Development—Hoai An Truong; Foundation—Cynthia Boyle; Honorary Chairman—Robert Beardsley; Trustees—Butch Henderson, David Russo, Neil Leikach, Speaker Ruth Blatt and Vice-Speaker Carol Stevenson. Their timeless efforts on our endeavors are genuinely appreciated.

...and to All Past Presidents of MPhA whose wisdom was always well taken.
...and Nancy, Administrative Assistant and our ASP student volunteers.

Finally, I assure you that your MPhA Board of Trustees will keep you abreast of our Kelly Memorial Building and UMMS and related developments. I will assure you that MPhA's best interests, now and long term will be our focal point.

THANK YOU for allowing me to serve you, MPhA, and our Pharmacy profession.

# Internet Drug Outlet Identification Program Criteria

## Patient Safety and Business Practice Standards

***Licensure and Residency***

The pharmacy, in accordance with applicable state and federal laws and regulations, must be licensed or registered in good standing to operate a pharmacy or engage in the practice of pharmacy in all applicable jurisdictions.

The pharmacy, in accordance with applicable state and federal laws and regulations, must not be or not have been subject to significant disciplinary action.

The pharmacy, in accordance with applicable state and federal laws and regulations, must be registered with Drug Enforcement Administration (DEA) if dispensing controlled substances.

The pharmacy, in accordance with applicable state and federal laws and regulations, must be domiciled in the United States.

***Prescriptions***

The pharmacy, in accordance with applicable state and federal laws and regulations, must assure the legitimacy and authenticity of all prescription drug orders. *A legitimate and authentic prescription drug order must be based upon a valid patient-prescriber relationship, which requires the following to have been established: a) The patient has a legitimate medical complaint; b) A face-to-face physical examination adequate to establish the legitimacy of the medical complaint has been performed by the prescribing practitioner or in the instances of telemedicine through a telemedicine practice approved by the appropriate Practitioner Board; and c) Some logical connection exists between the medical complaint, the medical history, and the physical examination and the drug prescribed.*

The pharmacy, in accordance with applicable state and federal laws and regulations, must adhere to the Federal Controlled Substances Act and DEA rules regarding prescriptions for controlled substances, including but not limited to the following: a) Prescriptions for Schedule II controlled substances must be provided in writing by the prescriber; b) Prescriptions for Schedule III - V controlled substances must be provided in writing by the patient or prescriber, or verbally or by facsimile by the prescriber; c) Schedule II controlled substance prescriptions may not be refilled; a new prescription must be issued for each quantity of the substance.

The pharmacy, in accordance with applicable state and federal laws and regulations, must *not* dispense or offer prescriptions originating from telephonic, electronic, or online medical consultations without a pre-existing patient-prescriber relationship that has included a face to face physical examination.

The pharmacy, in accordance with applicable state and federal laws and regulations must *not* offer to dispense or dispense medications that have not been approved by FDA.

***Patient Privacy***

The pharmacy, in accordance with applicable state and federal laws and regulations, must maintain a secure Web site and ensure patient identifiable information and prescription transactions are encrypted per industry standards.

The pharmacy, in accordance with applicable state and federal laws and regulations must have and provide patients with a statement of patients' rights to privacy and attempt to obtain from patients signed confirmation of receipt of such statement.

***Patient Services***

The pharmacy must provide, on the Web site, a 24-hour toll free number for patients who experience or believe they have experienced an adverse event involving their medication.

The pharmacy must provide, on the Web site, the US street address of the pharmacy that dispenses prescription medications on behalf of (or through) the Web site.

The pharmacy must provide, on the Web site, the US street address of the site's corporate headquarters or primary place of business.

The pharmacy must provide, on the Web site, instructions to patients describing how to submit complaints or concerns.

The pharmacy must offer pharmacist medication consultation via secure means through the Web site, via telephone, or in person for walk-in patients.

***Business Practices***

The pharmacy must attest and provide documentation to NABP that they obtain medications from US licensed wholesale drug distributors and/or US licensed or FDA registered pharmaceutical manufacturers.

The pharmacy must maintain a currently registered domain name that is not anonymous or private.

# Rx AND THE LAW

By Don R. McGuire Jr., R.Ph., J.D.

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## REPORTING OF PHARMACY CLAIMS

Recent newspaper articles have again focused public attention on the issue of prescription errors. While statistically, there is a very low error rate in pharmacy, the human cost of even one error is high. The Barker study[1] in 2003 placed the error rate in pharmacies at about 1.6%. With 3.7 billion prescriptions dispensed in 2006, that would equate to over 59 million errors per year. However, not all of these errors are potentially clinically important, that is, errors that could lead to patient harm or discomfort. Clinically important errors are the types of errors that turn into claims. They are also the focus of stories about prescription errors. The error rate here is just over 0.1%. This results in over 3.7 million clinically important errors per year.

One of these recent articles mentioned that most prescription errors go unreported. While the reports may not be made public, there are a number of legal requirements for the reporting of prescription mistakes. The timing and the form of the report varies from state to state. Some states require reporting by the pharmacist/pharmacy, while others require reporting by the health care professional's insurer. Some states require a report when a claim is opened, others when a claim is closed, and a few states require both an opening and a closing report. Let's examine a few examples to see the variations that exist today.

Iowa, Colorado, Kansas, New Mexico and North Carolina require the pharmacist or pharmacy involved in the claim to file a report. In Iowa, the pharmacist submits their incident report when the claim is closed. However, New Mexico requires a report when the claim is opened. North Carolina also requires an opening report, but only when the error involved resulted in death. Kansas takes a different approach. The pharmacy in Kansas creates a report that is kept on file in the pharmacy. It is not submitted to the board of pharmacy. The report is subject to review whenever a pharmacy board inspector calls on the pharmacy.

In many other states, the pharmacy's or the pharmacist's insurer is required to file a report. These reports are made to

1. National Observational Study of Prescription Dispensing Accuracy and Safety in 50 Pharmacies; E.A. Flynn, K.N. Barker, and B.J. Carnahan; Journal of the American Pharmaceutical Association; Vol. 43, No. 2; March/April 2003.

the board of pharmacy, the department of insurance, or both. Again, there is much variation from state to state. At least 12 states require the insurance company to file a closed report (some of these are done on an annual basis), while at least 6 states require both an open and closed report from the insurer. Many of the states requiring a closed claim do so only when a payment is made to the claimant. Nevada, for example, only requires a report if the payment is over $5,000. Texas goes a step further.

The insurer makes both an open and closed report to the board of pharmacy in Texas. Presumably the board is interested in knowing both the number of errors occurring in the state as well as the health care professionals who are involved. However, the insurance company is also required to make a report to the department of insurance if the payment is $10,000 or more. There is a separate, longer form to be used if the payment is over $25,000. The department of insurance is typically more concerned with the number of claims in the state and the dollar amounts paid. The department of insurance also monitors the availability of liability insurance for health care professionals in its state.

Reports submitted to the boards of pharmacy (by either the pharmacist or the insurance company) could result in some sort of disciplinary action against a pharmacy or a pharmacist. In most circumstances, the disciplinary action is a public record. As you can see, there are a number of reporting requirements for pharmacy errors even though a large number of them may not be disclosed to the public. For the practicing pharmacist, you need to be aware if there is a reporting requirement in your state. You can check the board's website or ask your inspector the next time they are in your store. Your insurance company will take care of all of the reports that they are required to file. Just remember that the insurer is legally required to file these reports, so don't ask them not to file it.

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*This article discusses general principles of law and risk management. It is not intended as legal advice. Pharmacists should consult their own attorneys and insurance companies for specific advice. Pharmacists should be familiar with policies and procedures of their employers and insurance companies, and act accordingly.*

## *Therapeutically Speaking...*

# Stay Tuned: Update on the Management of Hepatitis B Virus

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An estimated 350 million people worldwide are chronically infected with Hepatitis B Virus (HBV).[1] In the United States, an estimated 1.25 million people are hepatitis B carriers. Carriers are defined as individuals positive for hepatitis B surface antigen (HBsAg) for more than six months.[2,3,4] Patients with active HBV require treatment with antiviral medications, which significantly increases the risk for adverse drug reactions and drug interactions, which the patient may be unaware of. Counseling about adverse events and monitoring for drug interactions is an essential role for the community pharmacist. Pharmacists can play a vital role in the education of patients encountering initiation of complex HBV medications.

Carriers infected with this disease have an increased risk of developing cirrhosis, hepatic decompensation, and hepatocellular carcinoma.[5] Hepatic complications secondary to Hepatitis B infection occur in 15-40% of those chronically infected with the virus.[6] Therefore, the objective of treatment is to achieve sustained suppression of HBV replication, remission of liver disease, and prevention of cirrhosis, hepatic failure, and hepatocellular carcinoma.[6]

Hepatitis B Virus is transmitted through perinatal, percutaneous, person-to-person contact, intravenous drug use (IVDU) and sexual exposure.[3,4] Those at highest risk for contracting HBV are those of Asian descent since most are infected at birth or by an infected family member throughout various countries in Southeast Asia.[7] Others at high risk are men who have sex with men, IVDU, HIV-infected individuals, pregnant women, and those in close contact with HBV-infected individuals.[3,4] Dialysis patients are at high risk due to contamination of dialysis equipment or decreased response rate to Hepatitis B vaccination in patients with chronic renal failure and less durable response than the normal population.[8] Those between the ages of 20 and 49 have the highest risk of contracting HBV.[6] Thirty percent of those infected with HBV are asymptomatic. For those that are symptomatic, the most common symptoms include: jaundice; fatigue; abdominal pain; decreased oral intake; nausea and vomiting; and joint pain.[6]

Hepatitis B viral panels should be evaluated in patients at risk, or those presenting with symptoms. It is recommended patients such as those undergoing hemodialysis, individuals with HIV or Hepatitis C Virus, IVDU, pregnant women, household or sexual contacts of HBsAg (+) patients, and inmates should be screened. Hepatitis B panel requires careful interpretation. Table 1 defines diagnostic laboratory markers in a hepatitis B panel and Table 2 characterizes diagnostic markers with respect to time of presentation. Patients with chronic/active HBV are Hepatitis E antigen positive (HBeAg). When the antibody to Hepatitis E antigen appears the HBeAg becomes negative. Treatment and duration of treatment are dependent on the presence or absence of the HBeAg. Active infection is present when HBeAg is positive. The absence of the HBeAg is a marker of successful treatment. When HBeAg seroconverts from positive to negative for more than six months, treatment with oral agents may be discontinued.

**Table 1.** Interpretation of Laboratory Markers in Hepatitis B [10]

| Marker | Interpretation |
|---|---|
| Hepatitis B Surface Antigen<br>HBsAg | Earliest indicator of acute HBV<br>Disappears during recovery but immunocompromised may still have a (+) reading |
| Hepatitis B E Antigen<br>HbeAg | Only present when active virus present<br>Marker of infectivity<br>Marker of successful treatment (when HBeAg disappears anti-HBe appears) |
| Anti-hepatitis B core antigen<br>Anti-HBc | Indicates past infection<br>Remains positive for life |
| Hepatitis B E Antibody<br>Anti-HBe<br>Antibody to HbeAg | Appears as HBeAg disappears<br>Indicates successful treatment measures |

| | |
|---|---|
| Hepatitis B Surface Antibody<br>Anti-HBs | Indicates previous exposure to HBV, but the virus is no longer present and the person cannot pass on the virus to others<br>Indicates successful vaccination |
| HBV DNA | More sensitive than HBeAg for detecting virus in blood stream<br>Monitor antiviral therapy outcomes |

**Table 2.** Diagnostic Markers of HBV [11]

| Markers | Incubation (4-12 weeks) | Late Incubation/ Early Acute (1-2 weeks) | Early Acute (2-12 weeks) | Acute (2-12 weeks) | Acute/ Seroconversion in Progress (2-12 weeks) | Convalescent Window (12-24 weeks) | Early Recovery | Recovery (Years) |
|---|---|---|---|---|---|---|---|---|
| HBsAg | | X | X | X | X | | | |
| HBeAg | | | X | X | | | | |
| Anti-HBc | | | | X | X | X | X | X |
| Anti-HBe | | | | | X | X | X | X |
| Anti-HBs | | | | | | | X | X |

The objective of treatment is to achieve and maintain sustained suppression of HBV replication and prevent of hepatic complications.[6] HBeAg (+) patients with HBV DNA > 20,000 IU/mL and ALT > 2 times the upper limit of normal (ULN) should receive treatment. Treatment should be delayed for three to six months in newly diagnosed compensated liver disease, a condition where liver cells are damaged due to HBV but the liver continues to function, due to the possibility of spontaneous HBeAg seroconversion. Since HBeAg (-) patients often have more mutations or harder to treat virus strains, it is imperative to initiate treatment immediately and for longer periods of time.[12]

FDA-approved medications utilized to suppress HBV replication and minimize further medical complications include adefovir dipivoxil (Hepsera™), interferon alfa-2b, pegylated interferon alfa-2a (Pegasys™), lamivudine (Epivir, 3TC™), entecavir (Baraclude™), and telbivudine (Tyzeka™); refer to Table 3 for additional information. Cost, convenience, route of administration, patient characteristics, and medical comorbidities must be addressed prior to initiation of treatment.

**Table 3.** FDA Approved Medications Used in the Treatment of HBV[12]

| **Adefovir diplivoxil (Hepsera™)** | |
|---|---|
| Advantages | • Effective in suppressing wild-type and lamivudine-resistant HBV<br>• Administration without regard to meals |
| Disadvantages | • Slow viral suppression<br>• Minimum = 12 months |
| Mechanism | • Nucleotide analog (NA) that inhibits reverse transcriptase. |
| Dosing | • **CrCL ≥ 50 mg/ml**: 10 mg Daily<br>• **CrCL 20-49**= 10 mg every 48 hours<br>• **CrCL 10-19**= 10 mg every 72 hours<br>• **HD**: 10 mg every 7 days after dialysis |

| | |
|---|---|
| Adverse Effects | • Nephrotoxicity (high doses)<br>• Hematuria<br>• ↑ AST/ALT<br>• Weakness<br>• Headache<br>• Lactic acidosis |
| Drug Interactions | • Do not combine with known nephrotoxic agents<br>• Ganciclovir/Valganciclovir → Increased side effects<br>• Ribavirin→ Increased risk of hepatic decompensation, pancreatitis, or lactic acidosis |
| **Entecavir (Baraclude™)** | |
| Advantages | • In vitro→ More potent than lamivudine and adefovir<br>• Effective against lamivudine-resistant HBV<br>• Well-tolerated |
| Disadvantages | • Costly<br>• Administer on an empty stomach |
| Mechanism | • Nucleotide analog (NA) that inhibits reverse transcriptase |
| Dosing | • **CrCL ≥ 50 mg/ml**<br>o Lamivudine-naïve: 0.5 mg daily<br>o Lamivudine-experienced: 1 mg daily<br>• **CrCL 30-49**<br>o Lamivudine-naïve: 0.25 mg daily or 0.5 mg every 48 hours<br>o Lamivudine-experienced: 0.5 mg daily or 1 mg every 48 hours<br>• **CrCL 10-29**<br>o Lamivudine-naïve: 0.15 mg daily or 0.5 mg every 72 hours<br>o Lamivudine-experienced: 0.3 mg daily or 1 mg every 72 hours<br>• **CrCL < 10**<br>o Lamivudine-naïve: 0.05 mg daily or 0.5 mg every 7 days<br>o Lamivudine-experienced: 0.1 mg daily or 1 mg every 7 days<br>• **HD/CAPD**<br>o Lamivudine-naïve: 0.05 mg daily or 0.5 mg every 7 days<br>o Lamivudine-experienced: 0.1 mg daily or 1 mg every 7 days<br>o Give after dialysis |
| Adverse Effects | • ↑ AST/ALT<br>• Fatigue<br>• Headache<br>• Hematuria<br>• Hyperglycemia<br>• Lactic acidosis |
| Drug Interactions | • Ganciclovir/Valganciclovir→ Increased hematologic side effects<br>• Ribavirin→ Increased risk of hepatic decompensation, pancreatitis, or lactic acidosis |
| **Interferons** | |
| Advantages | • Finite duration of treatment<br>(4-6 months in HBeAG + 12 months in HBeAg -)<br>• Effective only in those<br>• Pegylated formulation preferred due to more convenient administration and more sustained viral suppression |
| Disadvantages | • Injection<br>• Extensive side effect profile<br>• Do not initiate in decompensated cirrhosis |

| | |
|---|---|
| Mechanism | • Antiviral, antiproliferative, and immunomodulatory |
| Dosing | • 5 MIU subcutaneously daily<br>• 10 MIU subcutaneously 3x/week<br>• Pegylated (Pegasys™) → 180 mcg subcutaneously every week<br>• Discontinue if SCr > 2 mg/dL<br>• Platelets < 50,000 → Decreased by 50%<br>• Platelets < 25,000 → Discontinue<br>• AST > 5 x ULN → Discontinue |
| Adverse Effects | • ↑ALT<br>• Anorexia<br>• Emotional lability<br>• Fatigue<br>• Hair loss<br>• Hypo/Hyperthyroid<br>• Influenza-like symptoms<br>• Liver decompensation<br>• Neutropenia<br>• Thrombocytopenia |
| Drug Interactions | • No clinically significant interactions |
| **Lamivudine (Epivir-HBV ™)** | |
| Advantages | • Well tolerated<br>• May be given without regard to food<br>• Low cost<br>• Co-infection with HIV |
| Disadvantages | • High incidence of resistance<br>• Minimum of 12 months in<br>• HBeAg (+)<br>• 6 months after seroconversion<br>• Indefinite in HBeAg (-) |
| Mechanism | • Nucleotide analog (NA) that inhibits reverse transcriptase |
| Dosing | • **CrCL ≥ 50 mg/ml:** 300 mg daily<br>• **CrCL 30-49**: 150 mg daily<br>• **CrCL 15-29**: 150 mg first dose, then 100 mg daily<br>• **CrCL 5-14**: 150 mg first dose, then 50 mg daily<br>• **CrCL <5**: 50mg first dose, then 25 mg daily |
| Adverse Effects | • ↑ALT<br>• Lactic acidosis |
| Drug Interactions | • Interferon → Increased risk of hepatic decompensation, pancreatitis, or lactic acidosis<br>• Ganciclovir/Valganciclovir → Increased hematologic side effects |
| **Telbivudine (Tyzeka ™)** | |
| Advantages | • May be given without regard to food |
| Disadvantages | • High rate of resistance<br>• Cross-resistant with lamivudine |
| Mechanism | • Nucleotide analog (NA) that inhibits reverse transcriptase |
| Dosing | • **CrCL ≥ 50 mg/ml**: 600 mg daily<br>• **CrCL 30-49**= 600 mg q48hours<br>• **CrCL < 30**= 600 mg q72hours<br>• **ESRD**= 600 mg q96hours |

| | |
|---|---|
| | • **HD**= Administer post-dialysis session |
| Adverse Effects | • ↑ CPK<br>• Abdominal pain<br>• Fatigue<br>• Headache<br>• Lactic acidosis<br>• Nasopharyngitis<br>• Nausea/vomiting<br>• URI<br>• Lactic acidosis |
| Drug Interactions | • No clinically significant interactions |

NA= Nucleoside Analog
AST= Aspartate Aminotransferase
ALT= Alanine Aminotransferase
CAPD= Continuous Ambulatory Peritoneal Dialysis
CrCL= Creatinine Clearance
MIU= Million International Units
CPK= Creatine Phosphokinase
ESRD= End Stage Renal Disease
HD= Hemodialysis
URI= Upper Respiratory Infection

Treatment may be initiated with any agent listed in Table 3 as long as patient characteristics, co-morbidities, and medications are considered. Successful seroconversion occurs in 12-27% of individuals receiving treatment for HBV at one year. Six months after discontinuation of treatment, HBeAg seroconversion rates increase slightly in patients who received pegIFN, whereas 20-50% of patients who received nucleoside analogues reverted back to HBeAg positivity.[6] PegIFN-α, adefovir, or entecavir are preferred for long-term treatment. Individuals with HIV co-infection should be initiated on lamivudine, a nucleoside analogue (NA), as it has activity against HBV and HIV. Although not FDA-approved for HIV and HBV co-infection, emtricitabine and tenofovir have been clinically evaluated as a successful treatment option in those co-infected. Individuals with decompensated cirrhosis must avoid initiation with interferon due to liver decompensation secondary to these agents. Patients who fail to respond to PegIFN-α may be started on a NA. Individuals who fail to respond by < 2 log decrease in serum HBV DNA after a minimum of 6 months of NA therapy should be switched to an alternative agent. Promising agents being investigated in the treatment of HBV include emtricitabine, tenofovir, and clevudine. Combination therapy has not proven to be superior to monotherapy in inducing a higher rate of sustained response and often results in increased cost, drug toxicities, and drug interactions.

Management requires regular follow-up every three to six months. If ALT levels become more elevated, patients should be monitored more frequently. Patients should also have HBV DNA levels drawn to assess baseline status and used to monitor treatment.

Pharmacists should counsel patients on pertinent adverse drug events and monitoring parameters of their therapy. They should also reemphasize the necessity for follow-up to assess treatment response and prevent or limit significant toxicities. It is important that renal dosing recommendations are followed to avoid drug toxicities. It should be stressed to patients the importance of compliance as successful treatment limits the risk of developing cirrhosis, hepatic decompensation, and hepatocellular carcinoma.

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# Discovery of Insulin

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The discovery of insulin is hailed as one of the most significant events in the history of the treatment of diabetes. The word diabetes is from the Greek word "to pass through" reflecting the polyuria symptom in people with diabetes. The Latin word "mellitus" was added centuries later, which meant honey, in recognition of the sweet tasting urine of people with diabetes[1]. Prior to the discovery of insulin, a diabetes diagnosis meant wasting away and certain death because no drug treatment was available. The Greek physician Arateus in the 1st Century referred to diabetes as "the melting down of flesh and limb into urine," referring to the weight loss, frequent urination, and complications such as limb amputations associated with the disease[1]. The only treatment for diabetes prior to insulin was starvation diets and an array of special diets[1]. These diets delayed death from diabetes by a few months, but many patients died of under-nutrition and starvation.

Frederick Banting and Charles Best are credited for the discovery of insulin in 1921 at the University of Toronto. Several investigators before Banting had been successful at preparing extracts of the pancreas that could lower blood sugar but impurities in the extract lead to toxic reactions preventing its use[2]. Banting believed the failed attempt by others was because the active substance was probably destroyed by the digestive enzymes in the acinar tissue of the pancreas during extraction of the whole gland[2]. Fueled with the idea that it was possible to isolate the internal secretions of the pancreas by ligating the pancreatic duct to induce atrophy of the acinar cells and thereby minimize the contamination of the tissue extract by the digestive enzymes, Banting began testing his hypothesis in the laboratory of John James Rickard Macleod, a professor of physiology and department head at the University of Toronto, with the assistance of Charles Best[2].

In the course of their experiments with dogs made diabetic by the removal of their pancreas, Banting and Best were able to make a pancreatic extract from grounded degenerated dog pancreas which had anti diabetic characteristics[3]. Their extract was successful in lowering the high blood sugar of the depancreatized dogs; however, impurities in the extract caused toxic reactions. James Bertram Collip, a biochemist, joined the team with the task of producing a purified form of the extract acceptable for human testing. The first clinical test of the pancreatic extract in humans, now made from whole beef pancreas, was conducted in January 11, 1922 and more patients were treated subsequently with favorable results[2].

The name "insulin" was given to the pancreatic extract and although it was not a cure for diabetes, the success of insulin to treat diabetes in humans gave hope to many people with diabetes and paved the way to a whole trend of research on insulin and diabetes treatment. Modern science and technology has lead to the evolution of production of insulin from cows and pigs to human insulin that can be mass produced through genetic engineering processes. To date, there are fast-acting, short-acting, intermediate-acting, and long-acting variations of insulin with consistent purity and potency, a considerable change from the "murky, light brown liquid" produced in the era of Banting and Best that had impurities and varied potency.

While efforts to make insulin available as an oral tablet have failed, it still remains as an invaluable tool in the treatment of uncontrolled diabetes. Millions of people living with diabetes today would probably have died at an early age without treatment with insulin. Looking back, we can see how the work of the team lead by Dr. Banting has contributed to our knowledge and treatment of diabetes.

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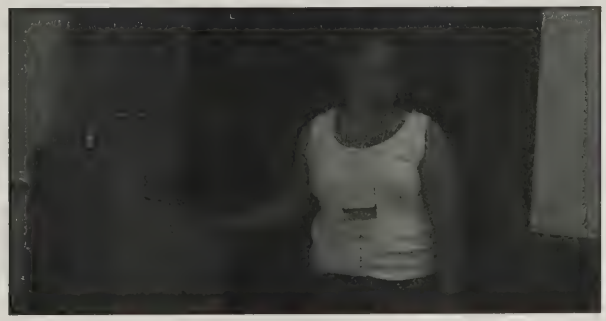
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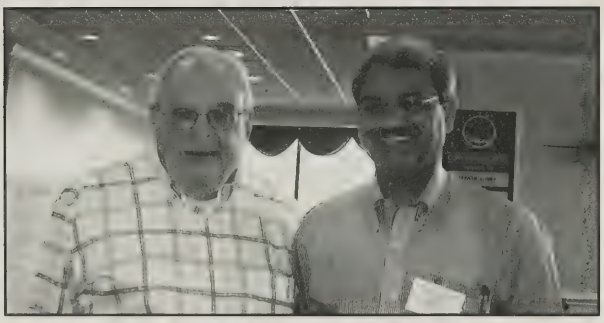
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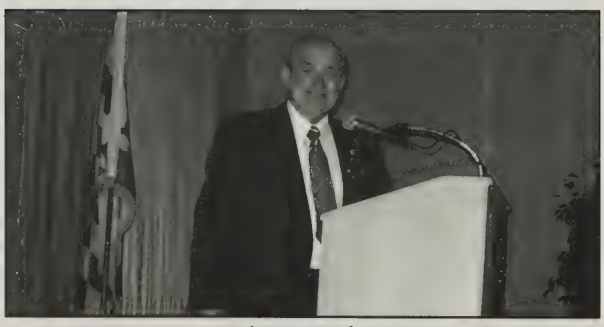
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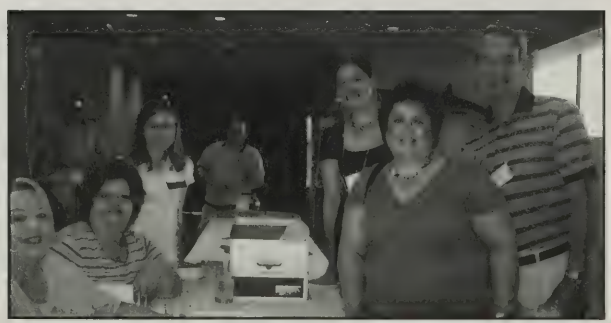
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# Continuing Education for Pharmacists

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## Challenges in Pharmacy Practice: Dispensing Errors and their Prevention

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**Goal**. The goal of this lesson is to define various dispensing errors in pharmacy practice and suggest recommendations on how to avoid and reduce them.

**Objectives**. At the conclusion of this lesson, successful participants should be able to:

1. recognize examples of dispensing errors and their extent of occurrence in pharmacy practice;
2. list major reasons why dispensing errors occur in community and institutional pharmacy practice; and
3. identify recommendations on how to reduce the incidence of dispensing errors.

### Background

Medical errors have been estimated to cost the nation between $17 and $29 billion each year, including additional health care spending, disability payments, and lost wages and productivity, with health care costs amounting to more than half of that total.



Gossel



Wuest

This lesson defines the terminology that describes errors. It emphasizes common causes of dispensing errors and identifies suggestions to reduce their occurrence. Additional causes along with their remedies for prevention will be discussed in another lesson in this series.

### Medical Errors

Prescription drug use is increasing in the United States. More than 60 percent of all U.S. adults aged 45 to 64 years during the span 1999 through 2000 reported the use of at least one prescribed medication. Coincident with this increasing rate are decreasing time and funding for health care professionals to focus on patient education. The potential contribution of these trends to the inherent danger of medication that is used improperly is reported in an Institute of Medicine (IOM) publication, which estimated that nearly half of American adults have difficulty in understanding and acting on health information.

Errors have been classified as those of *omission* (failure to act correctly) or *comission* (acted incorrectly). They can also be classed as potential or actual. A *potential* error would be a mistake that is detected and therefore corrected before the actual error is made. An *actual* error is one that is not detected; thus, an inappropriate action is taken. Dispensing errors can also be either mechanical or judgmental. A *mechanical* error is made by dispensing an incorrect drug, or an improper strength or dosage form. Mechanical errors are estimated to represent more than 80 percent of insurance liability claims. A *judgmental* error occurs when mistakes are made during a drug utilization review, patient counseling session, or therapeutic drug monitoring.

### Dispensing Errors

One type of medical error, dispensing errors, are those made by the pharmacy staff. For this definition, it is assumed that the prescription or medication order, when received, is correct. In its most elemental form, a dispensing error has been defined by one author as any deviation from the prescriber's order, or any mistake made but not detected until after the item has left the pharmacy. Since it is the pharmacist who is most intimately concerned with accuracy of what is dispensed, and who has final authority for approving prescription correctness, a misfill remains his or her responsibility.

This definition can be deceiving, though, since an error in dispensing may originate at the prescribing level. For example, a physician may issue a prescription that contains no errors, but the writing is illegible. If a pharmacist interprets the prescription incorrectly and dispenses the wrong medication, the cause of the actual error could be interpreted in its broadest sense as a medical rather than dispensing error since

**Table 1**
**Examples of Abbreviations That Can Cause Dispensing Errors***

| Abbreviation | Intended to Mean | Misread As | Recommendation |
|---|---|---|---|
| / | Separate doses or *per* | The numeral "1" | Write *per* |
| + | *Plus* or *and* | The numeral "4" | Write *and* |
| >, < | Greater than, less than | The opposite intended | Write out full meaning |
| µg | Microgram | Milligram (mg) | Use *mcg* or write *microgram* |
| AU, AS, AD | Both ears, left ear, right ear | OU, OS, OD (both, left, right eyes) | Write out full meaning |
| cc | Cubic centimeters | *U* (units) | Use *mL* |
| D/C | Discharge or discontinue | The opposite that is intended (i.e., discharge meds are discontinued) | Write out full meaning |
| HS | Half strength | At bedtime | Write med strength |
| q hs, q 6 PM | Nightly at bedtime, at 6:00 p.m. | Every hour, every 6 hours | Use *hs* or write out |
| q.d., Q.D.** | Every day | Four times daily (qid) | Write *daily* |
| q.o.d., Q.O.D.** | Every other day | *qd* or *QD* or *qid* | Use *q other day* or write *every other day* |
| SC, SQ | Subcutaneous | *SL* (sublingual) | Write out full meaning |
| ss | *one-half* | The number "55" | Use "1/2" or write *one-half* |
| TIW | Three times a week | Three times a day or twice a week | Write out completely |
| U** | Unit(s) | The numerals 0, 4 or cc | Write *unit(s)* |
| x3d | For three days | For three doses | Write *for 3 days* |
| IU** | International Unit(s) | IV (intravenous) or "10" | Write *international unit(s)* |
| BT | Bedtime | *BID* (twice daily) | Write *bedtime* |
| o.d. or OD | Once daily | *right eye*, leading to oral meds used in the eye | Write *daily* |
| OJ | Orange juice | *right or left eye*, leading to drugs that are to be diluted in orange juice are used in the eye(s) | Write *orange juice* |
| per os | By mouth, orally | *left eye* | Write *PO*, *by mouth*, or *orally* |
| SSRI | Sliding scale regular insulin | *Selective serotonin reuptake inhibitor* | Write *sliding scale (insulin)* |
| MgSO4** | Magnesium sulfate | *Morphine sulfate* | Write complete name |
| MS, MSO4** | Morphine sulfate | *Magnesium sulfate* | Write complete name |

*For a comprehensive list visit www.ismp.org/Tools/errorproneabbreviations.pdf.
**These abbreviations are included in JCAHO's list of "dangerous abbreviations" that must be included in an organization's "Do Not Use" list. See Burkiewicz JS, Hassenplug KL. *J Pharm Technol.* 2006;22:332.

the prescriber's sloppy handwriting led to the mistake.

An analysis of dispensing errors in the U.K.'s National Health Service hospitals has been published. The most common mistakes identified from 7,158 error reports included dispensing the wrong medication (23 percent), supplying the wrong strength of the correct drug (23 percent), listing the wrong directions (10 percent), and dispensing the wrong quantity (10 percent).

Dispensing errors are a problem in the United States, with estimates of occurrence ranging from 3 to 12 percent of prescriptions filled in community pharmacies. About 1.5 percent of these are reported to be potentially serious. One study undertaken in 50 community pharmacies found about four errors per day in a pharmacy filling 250 prescriptions daily. At this rate it was projected that 51.5 million errors occur across the nation during the filling of three billion prescriptions each year.

It is appropriate to discuss dispensing errors in terms of the "five rights" of drug administration: the right *patient*, right *drug*, right *dose*, right *route*, and right *time*. An error in any of these can result in an adverse drug event. Assuring that these elements are maintained correctly is the ultimate goal in the dispensing of all medications. Keeping this forefront in the dispensing pharmacist's mind is an easy first step toward preventing errors. When an error occurs, key questions to prevent recurrence include: what went wrong, and how and why did it happen?

**Communication Issues**

There is a significant potential for error as soon as the pharmacy receives a prescription. The typical cause of errors at this early stage can often be a breakdown in communication. Many errors reportedly occur as a result of poor verbal or written communication. Improving communication skills with other members of the health care team and with patients can reduce errors.

**Illegible Handwriting.** Illegible handwriting by the prescriber is a cause of error. For example, drug names ending with the letter "L" can cause an error when there is insufficient space between the drug name and its intended dose. Examples include "Inderal10 mg," which may be read incorrectly as "Inderal 110 mg" and "Medrol4 mg," which may be read incorrectly as "Medrol 14 mg." Adequate spacing between the drug name and the dose is crucial on all prescriptions and medication order forms, and electronic formats such as the pharmacy computer, computer-generated medication administration records, and computerized order entry systems.

Misplaced zeroes and unclear or missing decimal points are common causes of *tenfold errors* in medication dosing, despite being a well-recognized risk, particularly in pediatric patients. An evaluation of 200 consecutively detected medication orders with tenfold errors in dosing in a 631-bed tertiary-care teaching hospital showed these errors are produced by a misplaced decimal point 43.5 percent of the time, adding an extra zero in 31.5 percent of cases, and omitting a zero in 25 percent of cases. Forty-five percent of the errors were rated potentially serious or severe; 19.5 percent of the errors occurred in pediatric patients. Levothyroxine accounted for 19 percent of all errors.

Decimal points that are not clearly visible on a prescription for doses written with a trailing zero, such as "Prednisone 5.0 mg," has been misinterpreted as "Prednisone 50 mg" with a consequent tenfold error in dosing. Trailing zeros should not be used for drugs with doses expressed in whole numbers. Failure to include a zero before a decimal point when the dose is less than a whole unit can also result in a similar tenfold dose increase. For example, a prescription for "Synthroid .1 mg" may be misread as "Synthroid 1 mg."

**Medical Abbreviations and Symbols.** Abbreviations, symbols and other shorthand notations used on prescriptions and medical records have been misinterpreted. The abbreviation "HCTZ" for hydrochlorothiazide has been confused for hydrocortisone, "MTX" for methotrexate has been confused with mitoxantrone, and "T3" intended for Tylenol #3 has been mistaken for liothyronine. Such confusion most likely could occur when a pharmacist who is new to an area is unfamiliar with such notations that are common to that particular geographic site.

Some abbreviations should never be used. Confusion over "MgSO4" (for magnesium sulfate) and "MSO4" (for morphine sulfate) has led to serious errors. These abbreviations (and all medical shorthand notations) should, ideally, be eliminated, and drug names and their instructions for use written out in their entirety.

Table 1 provides a sampling of potentially harmful abbreviations that should be avoided in all forms of medical communications. This includes abbreviations that are on the "Do-Not-Use" list sanctioned by The Joint Commission (formerly the Joint Commission on Accreditation of Healthcare Organizations or JCAHO). Error-prone abbreviations should not be used, even in printed material for several reasons. They can be misinterpreted. They may be copied into handwritten orders, where they are likely to be confused. Moreover, using them in print perpetuates the idea that they are acceptable.

Complete names of drugs and their instructions for use should be used when transcribing verbal instructions. Reading back what has been transcribed will help prevent errors with drug names or numbers that are similar sounding. All abbreviations that have the potential to cause an error should be clarified. Ambiguous or incomplete orders should be questioned to protect the patient.

**Drug/Product-Related Issues.** Drug products with similar sounding names may be a cause for dispensing errors. About 15 percent of errors reported to the U.S. Pharmacopeia Medication Errors Reporting Program are due to confusion over look-alike or sound-alike drug names. More than 750 drug names have been identified as potential causes of confusion with one or more other drugs. The problem is intensified when drugs with similar-sounding names are also available in similar dosage forms and strengths. Examples include diazepam and Ditropan, both available as 5 mg tablets; and Lanoxin and Levoxyl, both available as 0.125 mg tablets.

Errors from mix-ups with sound-alike drug names can be prevented by reading written prescriptions carefully and repeating back verbal orders. These are important first steps in the process of eliminating dispensing errors. Knowing the intended use can help in selecting the correct medication. The pharmacist can tactfully ask the patient the purpose for which the drug was prescribed and note this on the prescription record and prescription label.

**Developing Safer Dispensing Systems**

There are many steps from "pen to patient" that can contribute to medical errors. Dispensing errors are often the result of one or more breakdowns in the system, rather than carelessness of a single health care professional. A number of organizations have looked into the problem and suggested potential solutions. One, the National Coordinating Council for Medication Error

**Table 2**
**Recommendations for Enhancing Accuracy of Dispensing Medications**

The Council recommends:

1. ...prescriptions/orders always be reviewed by a pharmacist prior to dispensing. Any orders that are incomplete, illegible, or of any other concern should be clarified using an established process for resolving questions.
2. ...patient profiles be current and contain adequate information that allows the pharmacist to assess the appropriateness of a prescription/order.
3. ...the dispensing area be properly designed to prevent errors. Design should address fatigue-reducing environmental conditions (e.g., adequate lighting, air conditioning, noise level abatement, ergonomic fixtures); minimize distractions (e.g., telephone and personnel interruptions, clutter, unrelated tasks); and provide sufficient staffing and other resources for workload.
4. ...product inventory be arranged to help differentiate medications from one another. This may include the use of visual discriminators such as signs or markers. This is particularly important when confusion exists between or among strengths, similar looking labels, and names that sound or appear similar.
5. ...a series of checks be established to assess the accuracy of the dispensing process prior to the medication being provided to the patient. Whenever possible, an independent check by a second individual should be used. Other methods of checking include the use of automation (e.g., bar coding systems), computer systems, and patient profiles.
6. ...labels be read at least three times (e.g., when selecting the product, when packaging the product, and when returning the product to the shelf).
7. ...pharmacy staff triple check replenishment of regular medication stock or automated dispensing machines/cabinets (e.g., Pyxis, etc.) to ensure accuracy of product and precision of placement (e.g., when selecting the product, before the product leaves the pharmacy, and prior to placing the product in the automated dispensing machine/cabinet).
8. ...pharmacists counsel patients at the time of dispensing. Counseling should be viewed as an opportunity to verify the accuracy of dispensing and the patient's understanding of proper medication use. Counseling should include:
   - Indications for the use of the medication as well as precautions and warnings;
   - Expected outcome from the medication;
   - Potential adverse reactions and interactions with food or other medications;
   - Actions to take when adverse reactions or interactions occur; and
   - Storage requirements of the medication.
9. ...pharmacies collect and analyze data regarding actual and potential errors for the purpose of continuous quality improvement (e.g., provide feedback to local prescribers, provide error information to national reporting programs/databases).
10. ...both initial and ongoing training of pharmacy staff on accepted standards of practice related to accurate dispensing processes with the ultimate goal of medication error reduction.
11. ...each pharmacy establish policies and procedures for the medication dispensing process. This will ensure that all personnel, including pharmacists, support staff, and relief staff, are informed of expectations related to the dispensing process.

© 1998-2007 National Coordinating Council for Medication Error Reporting and Prevention

Reporting and Prevention (NCC MERP), has stated that in order for the error rate to be reduced, attention needs to focus on developing safer dispensing systems. Technology must be evaluated regularly to assure it is meeting current needs. The goal is to design safe systems in an environment where it is difficult to generate an error and where the system provides mechanisms to detect and correct errors.

The Institute for Safe Medication Practices (ISMP) has, among its several medication error prevention efforts, a voluntary practitioner error reporting program to learn about errors happening across the country, understand their causes, and share "lessons" learned. Additional information can be found at www.ismp.org.

**Recommendations**

The NCC MERP has published its recommendations to enhance accuracy of dispensing medications (Table 2). These recommendations apply to both hospital and community pharmacy practices.

**Overview and Summary**

While pharmacists explore new opportunities to expand their roles, prescription dispensing remains the cornerstone of pharmacy practice. Maintaining top-notch quality in prescription dispensing accuracy is a notable challenge, especially as the volume of prescriptions dispensed continues to rise, the complexity of drug therapy increases, and the overall demands on pharmacists intensify.

*The content of this lesson was developed by the Ohio Pharmacists Foundation, UPN: 129-000-08-001-H05-P. Participants should not seek credit for duplicate content.*

# Continuing Education Quiz

This month's questions are taken from the article on "Challenges in Pharmacy Practice: Dispensing Errors and Their Prevention". Circle your answers to the following questions and mail the entire page to Maryland Pharmacist CE, 650 W. Lombard Street, Baltimore, MD 21201-1572. There is no charge for this quiz for MPhA members (non-members $ 10.00). The completed quiz for this issue must be received by 1/15/11. A continuing education certificate for one and one-half contact hours (0.15 CEUs) will be mailed to you within six to eight weeks. Please type or print clearly. ACPE# 129-144-07-012-H05-P

**Name**_____

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(*Required*)

The Maryland Pharmacy Continuing Education Coordinating Council is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing education for pharmacists.

1. From 1999 through 2000, the percentage of U.S. adults aged 45 to 64 years who had reportedly used at least one prescribed medication was:
   a. more than 60 percent.
   b. more than 70 percent.
   c. more than 80 percent.
   d. more than 90 percent.

2. The Institute of Medicine estimates that American adults having difficulty understanding and acting on health information is:
   a. nearly one fourth.
   b. nearly one third.
   c. nearly one half.
   d. nearly all.

3. An error in dispensing an incorrect drug, or improper strength or dosage form is referred to as a:
   a. judgmental error.
   b. mechanical error.

4. The estimated occurrence of dispensing errors in prescriptions filled in U.S. community pharmacies is:
   a. 33 to 42 percent.
   b. 23 to 32 percent.
   c. 13 to 22 percent.
   d. 3 to 12 percent.

5. All of the following abbreviations are included in The Joint Commission's list of "dangerous abbreviations" that must be included in an organization's "Do Not Use" list EXCEPT:
   a. q.o.d.
   b. U.
   c. MgSO4.
   d. prn.

6. One study involving 50 community pharmacies, found about four errors per day in a pharmacy filling 250 prescriptions daily, which the investigators projected to how many errors in the filling of three billion prescriptions nationwide?
   a. 51.5 million
   b. 41.5 million
   c. 31.5 million
   d. 21.5 million

7. In an evaluation of detected medication orders with tenfold errors in dosing in a teaching hospital,which of the following produced the greatest number of errors?
   a. Adding an extra zero
   b. Omitting a zero
   c. A misplaced decimal point

8. Which of the following drugs accounted for the highest percentage of all errors described in the study in question # 7?
   a. Prednisone
   b. Levothyroxine
   c. Digoxin
   d. Amitriptyline

9. The U.S. Pharmacopeia Medication Errors Reporting Program has reported which of the following percentages of errors due to look-alike, sound-alike drug names.
   a. About 1.5 percent
   b. About 5 percent
   c. About 7.5 percent
   d. About 15 percent

10. Additional information on understanding causes of medication errors and sharing lessons learned can be found on which of the following websites.
   a. www.drugs@fda.gov
   b. www. ismp.org
   c. www.jcaho.gov
   d. www.nccmerp.org

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*The Official Publication of the Maryland Pharmacists Association*


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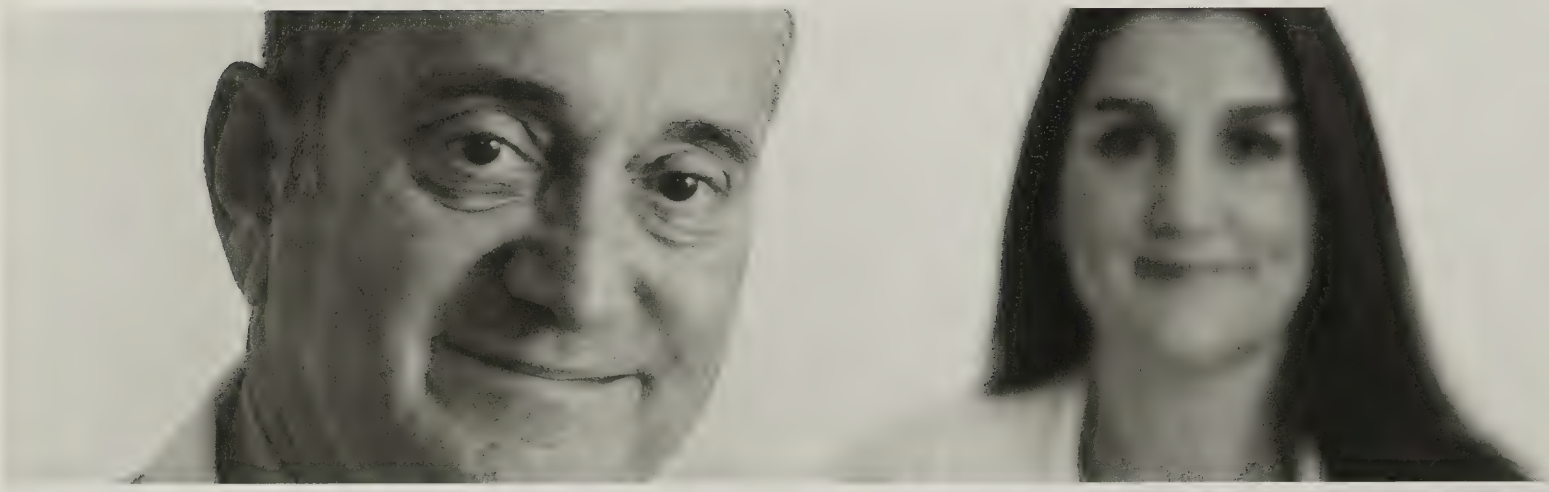

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# Presidents' Message: This is Our Time, Let's Seize the Opportunity!



Magaly Rodriguez de Bittner, Pharm.D.
President

*Many people have asked me what is my presidential theme for the year? What are my goals? I have actually been thinking about this for a long time and going thru a long list of goals and themes. I thought about quoting books, famous people, philosophers... but I have decided that the best fitting theme is:* ***This is our time, let's seize the opportunity!***

To accomplish this, I have three major goals that I have set for myself and MPhA for the next year.

## Strengthening the Association: It is time for a Dynamic and Stronger MPhA

It is every President's goals to make the Association stronger. Our Association is strong today due to our members and past leadership. Every past President has left his/her mark in our Association. This year, we have a unique opportunity to strengthen our organization. The sale of our beloved Kelly building will provide the opportunity to acquire economic resources to fortify the infrastructure of the organization and our museum.

Additionally, we have the talent to move our organization ahead. The environment in Maryland is embracing the new role of the pharmacists in the health care team, such as: P3, Immunizations, MTM, the PBM bills, etc. We have gained new ground in reimbursement for these services and have seen small increases in new practitioners who are buying their own pharmacies and employed pharmacists (in all health care settings) taking the profession of pharmacy in their own hands. We must maximize these efforts to strengthen MPhA. We have the talent and expertise to achieve this goal!

## Increase Patients and Health Care Providers Understanding of the Role of the Pharmacist

It is my goal to create a dialogue with the public, health organizations in the state and government and policy agencies concerning the role of the pharmacist. It is time to educate our patients about what happens behind the counter when they bring a prescription to a pharmacy or when they receive medications from a health system pharmacist. We must collaborate with other healthcare professional organizations and public/private agencies to position the pharmacist as the "medication expert".

## Empowering Pharmacists to Act Now: Seize the Time and the Opportunities

It is critical that we continue the work that we have started to provide pharmacists with the resources they need to do their job but also to continue to create new opportunities and shape the practice of Pharmacy. In the past two years, we have been instrumental in providing leadership with collaborative practice, the Maryland P3, MTM training, CE at midyear and annual meetings, immunizations and PBM bills just to mention some. MPhA has emerged as a leader and resource for our pharmacists by providing new skills and opportunities. We must empower pharmacists to take responsibility to define their profession not to allow others to define it.

We can not afford to say any longer that one of the barriers we face for expansion of P3 or MTM is the fact that we do not have enough pharmacists embracing these efforts to meet the demands of the employers or health plans. We must empower pharmacist to fully embrace these opportunities!

# toxtidbits

the maryland poison center's monthly update, news, advances, information. . . July 2008

## Brown Recluse Spider Envenomations

Insects and spiders proliferate following a wet and mild spring, with this year being no exception. Concerns over reactions to spider bites follows with special attention to the notorious brown recluse spider (*Loxosceles reclusa*) well known for its ability to cause necrotic lesions. The diagnosis of spider envenomation is usually based on clinical presentation without confirmation since patients rarely produce the offending spider. Brown recluse spiders are small brown spiders characterized by an upside down violin on the head , flat bodies, and only 6 eyes. They are endemic only to the south-central portion of the United States and rarely are transported to other areas. Bites from the brown recluse vary in severity from little or no reaction to severe dermal necrotic lesions occasionally accompanied with systemic symptoms. Many bites go unnoticed until intense pain and formation of a small white or hemorrhagic vesicle surrounded by swelling occurs about 8 hours later. The enzyme sphingomyelinase D, one of eight components is thought to be the main contributor to the cytotoxic and hemolytic properties of the venom. More severe envenomations are characterized by the formation over 24 to 72 hours of a blue gray colored 'sinking' lesion surrounded by a larger irregular shaped area of alternating blanching and redness. With severe bites, the center lesion forms an eschar that falls off revealing necrosis of deeper tissues. Although 90-95% of bites heal without complications there are some cases involving surgical debridement that may require several months to heal. Necrotic lesions can be caused by bacterial (staphylococcus [MRSA], streptococcus, gonococcus, and cutaneous anthrax), viral or fungal infections. Bites from a variety of arthropods as well as a host of medical and toxicological issues can result in a similar appearance. Misdiagnosis of necrotic lesions can lead to a delay in appropriate treatment. Treatment of brown recluse spider bites consists of tetanus prophylaxis, wound care, pain management, antibiotics for secondary infections, and supportive care. Lack of evidence of efficacy or potential side effects have limited use of other treatments utilized in the past. *Paul Starr, Pharm.D., CSPI*



***DID YOU KNOW THAT... brown recluse spiders are not indigenous to Maryland?***
Brown recluse spiders are found throughout the south central states of the U.S. (see map, dark shading). The spiders are **not** found in Maryland because they cannot survive Maryland winters. The possibility exists of brown recluse spiders being introduced through shipments from other areas of the country, but infestations are unlikely to occur.



Maryland Poison Center
University of Maryland School of Pharmacy

1-800-222-1222

Send any comments or questions to: toxtidbits,
410-706-7184 (fax) or Lbooze@rx.umaryland.edu

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# The History of Inhaled Anesthetics

Michelle Taymuree, Pharm.D. 2008

A modern day operating room is a sterile place. Great care is taken to reduce the possibility of infections. While the surgeon and his team are operating, the patient is resting comfortably or completely unconscious because of anesthesia. However, operating rooms were not always places of sterility and tranquility for patients. For many centuries, dating back to Hippocrates, operating rooms were places of extreme pain. In his texts, Hippocrates was more concerned that his patients remained still and did not turn away. He was less concerned with the excruciating pain experienced during the procedures.[1] Many people suffered with their ailments rather than have an operation; they were paralyzed with fear of the procedure and the horrific pain during and after the operation. Additionally, many people who actually braved the operation, suffered long after the procedure was completed; they were utterly traumatized by the experience inside of the operating room.[2]

Surprisingly, in textbooks published as recently as 1844 (just 2 years before general anesthesia would become commonplace), the perceived need to ameliorate a patient's pain level in the operating room was very low.[3] Prior to the development of general anesthesia, opium and alcohol and even the unconventional hypnotism were used in an effort to provide some pain relief for the patient; however, these methods were not always reliable and produced varying levels of pain control. Thus, surgeons aimed to work as quickly as possible; quicker procedures in the very least would reduce the amount of time a patient would be in extreme pain.[2]

However, the real impetus to improve the conditions in the operating rooms was the death rate associated with surgical procedures. Patient mortality following and during operating procedures was as high as 50%. The constant squirming and fidgeting, and screaming and crying were very distracting to the surgeon and left patient completely exhausted. This was surely contributing to the high mortality rates. After months of experimentation and failures, on October 16, 1846, in Boston MA, William T. G. Morton successfully demonstrated the use of ether via inhalation for general anesthesia. At the time however, Morton did not know the substance was ether! By November, Oliver Wendell Holmes, in a letter to Morton, suggested the name anesthesia—derived from Greek to mean without perception.[2] The notion that a surgical procedure could take place with the patient resting comfortably was remarkable and *rapidly* adapted by the medical community. Even without more experience or better guidance on how to use the ether (and the necessary precautions with this very volatile substance), in a mere 63 days after Morton's demonstration, dentists in London were placing their patients under general anesthesia during painful tooth extractions.

Shortly after the discovery of ether as an inhaled anesthetic, the quest to find different agents, that would not pose such a fire hazard, began. In addition to being flammable other drawbacks of ether included a prolonged induction, a disturbing odor and high incidence of nausea and vomiting post-op. However an extremely large advantage of ether was it was relatively safe to use and overdoses leading to fatality with ether were extremely rare.[4] Other agents began to immerge, one of them being chloroform. Chloroform showed great potential initially, as it was not flammable. However, slowly as reports began to immerge over the years of otherwise healthy patients suddenly dying in the midst of an operation, the safety profile of chloroform was thrown into question. After an exhaustive review, A. Goodman Levy demonstrated in animal studies that chloroform and adrenaline produced a fatal combination resulting in ventricular fibrillation, a deadly heart rhythm. Chloroform's use declined sharply thereafter.[5]

Nitrous oxide was another agent that was reintroduced after the introduction of ether. However, nitrous oxide was not readily accepted due to the first public demonstration of its use in 1844- the experiment failed miserably. However, a man named Gardner Q. Colton, who was actually present at the 1844 public failure, began using this gas on

his dental patients in 1864. Nearly 200,000 patients were treated with nitrous oxide without any fatalities. Thus, by 1867 (and a successful public demonstration) nitrous oxide use began to spread over the globe.[6] After manipulating how to administer the nitrous oxide (ultimately with oxygen), it is still a widely used inhaled anesthetic to this day.

Other successful inhaled anesthetic agents include the fluorinated hydrocarbons. Initially the fluorinated hydrocarbons were extensively used as coolants. However, in the quest to make flammable anesthetics nonflammable, the notion to fluorinate came about. With ties to Baltimore as a University of Maryland professor and the former director of Pharmacologic Research at the Maryland Psychiatric Research Center, John C. Krantz took the flammable anesthetic, vinamar and fluorinated it. The first man ever to receive a fluorinated anesthetic was Max Sadove and the experiment was a success, as Sadove fell into an unconscious state quickly and awoke a short time latter.[7] However, the formulation that Sadove received in 1953, known as fluroxene, is no longer used because of a toxic effect—fluminant hepatic necrosis. Other formulations, however, such as isoflurane are still apart of practice. The last inhaled anesthetic was introduced in the late 1980s and was a fluorinated agent, known as sevoflurane.

What is an acceptable level of pain for a patient to experience has dramatically changed in the past 150 years or so. The operating room has seen a vast transformation in a relatively short period of time. Now, patients have no perception of what occurs while in an operating room. Additionally, patients are able to control their pain levels after surgeries via medications they can administer to themselves. In today's society an acceptable level of pain is very patient specific. Pain is not ignored and a patient's comfort is a cornerstone of quality care. The birth of anesthesia helped change the landscape of surgical procedures—from a place of horrors to a place of unconsciousness.

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# "Therapeutically Speaking..." Health Literacy Issues to Consider in Pharmacy Practice

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*Have you ever taken the time to read the patient information leaflet about a medication that accompanies a prescription? Whether you are in a practice setting that is involved in the preparation of prescription medications or you have personally obtained a prescription within the past several years, you probably are aware of this piece of information. What you may not be aware of is that this information, which is often written at a tenth grade level or higher, is often not understood by millions of Americans who have limited health literacy.*

The Institute of Medicine defines health literacy as "The degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions."[1] Health literacy is a shared function of education, cultural and social factors, and health services. While reading, writing, and math skills comprise part of the basis of health literacy, many other skills and abilities are also important, such as speaking, listening, having adequate background information, and being able to advocate for oneself in the health system. Health literacy is increasingly vital to assist people in navigating a complex health care system and better manage their own health.[2]

An estimated one-third to one-half of adults in the United States, as many as 90 million Americans, possess limited health literacy skills, and may have difficulty understanding and acting on health materials. Information in less familiar print contexts, such as prescription container labels, may be confusing and more difficult to comprehend for less literate patients.[3] Studies suggest that while individuals with limited health literacy have a variety of backgrounds, the problem of limited health literacy is greater among older adults, minorities, people with limited education and those with limited English.[4, 5, 6] For individuals whose native language is not English, issues of health literacy are compounded by issues of basic communication and the specialized vocabulary used to convey health information.[1]

Differences in the ability to read and understand materials related to personal health also appear to contribute to health disparities. People with low health literacy are more likely to report poor health, have an incomplete understanding of their health problems and treatment, and be at greater risk of hospitalization.[7] Other factors that can contribute to health care disparities include lack of access to information, communication technologies, health care and supporting social services as well as lower education and lower socioeconomic status.[2]

Low health literacy is a major source of economic inefficiency in the U.S. healthcare system.[8] The cost of low health literacy to the U.S. economy is estimated to be in the range of $106 billion to $238 billion annually (which represents between 7-17% of all personal healthcare expenditures). If you take into account the future costs of low health literacy that result from current actions (or lack of action), the real present day cost of low health literacy is closer in range to $1.6 trillion to $3.6 trillion. The direct medical costs of low functional literacy are financed through additional hospital and office visits, longer hospital stays, extra tests, procedures and prescriptions.[9] These costs affect payers (who fund these additional resources) as well as taxpayers (who finance a disproportionate share through Medicaid and Medicare resources).

The Committee on Health Literacy was formed to bring together practitioners and professionals working in the field of low health literacy in order to focus on health literacy challenges and to advance solutions in a coordinated manner.[10] This committee developed a framework for health literacy which identifies three major areas of potential intervention

and forms the organizational principle for the report *Health Literacy: A Prescription to End Confusion.*[1] This framework, found in Figure 1, illustrates the potential influence on health literacy as individuals interact with educational systems, health systems, and cultural and social factors and suggests that these factors may ultimately contribute to health outcomes and costs. There is limited research on the potential causal relationships that the three elements of culture and society, education system and health system have on patient health outcomes and costs of this framework or model. Research of this type in the future should include all aspects of the health system, including pharmacy practice settings.

Public and private efforts have been identified in two areas as needing to occur to close the gap in health literacy (in order to provide fairness and equity in the health care system and to reduce health disparities).[2] The first effort is the development of appropriate written materials which are in plain language as well as effective, culturally and linguistically appropriate. There are many materials available to assist with writing materials of this type.[11, 12] The second effort is moving towards the goal of improving the skills of those persons with limited literacy. Many organizations such as public and medical libraries, voluntary, professional, and community groups, and schools can and do offer health literacy programs that provide skill improvement for low-literacy and limited English proficient individuals.[2]

Health care providers have an opportunity to actively participate in the improvement of health literacy of the population. Unfortunately, many practitioners in the health care industry often do not recognize the literacy constraints of their patients. Physicians are often surprised at the poor reading skills of some of their most poised and articulate patients. Many research describe low literacy as a silent epidemic as many physicians and other health care workers are not aware that their patients may have reading problems.[13]

Pharmacists see patients much more frequently than other health care providers and may be able to detect issues regarding patient health care literacy. Patients feel comfortable talking with pharmacists that they have an established and trusting relationship with and therefore some may be forthright in discussing their difficulties with comprehension of health care services and information. Pharmacists can serve as an effective member of the health care team in not only recognizing this issue, but working with patients in a respectful manner to ensure that patients can understand the most important aspects of their medication administration.

As a health care provider, pharmacists can create a "shame-free" environment where low-literate patients can seek help without feeling stigmatized.[14, 15] Pharmacists can utilize their expert medication knowledge to supplement any written medication information with verbal communication. Effective communication techniques, such as listening to the patient to learn about their concerns, utilizing commonly understood words and visual tools (i.e., pictures, pictorial illustrations, videotapes/DVDs) and not providing too much information in one counseling session, can assist with all patient communication.

Pharmacists and student pharmacists should utilize the "Teach-back" method[16] with all patients by incorporating the questions of the Indian Health Service model.[17] The Indian Health Service model is a reliable method to determine to what extent a patient understands the instructions for taking a medication. The three prime questions for new prescriptions using the Indian Health Service model are (1) What did your doctor tell you about this medication?; (2) How did your doctor tell you to take the medication?; and (3) What did your doctor tell you to expect? For refill prescriptions, the three prime questions for patients are: (1) What are you using this medication to treat?; (2) How do you take this medication?; and (3) What problems are you experiencing with this medication? The "Teach-back" method consists of asking the patient to repeat in their own words what they need to do with regards to their medication(s) (or any other health/medical care issues). If patients are not able to communicate what they should be doing after utilizing the "Teach-back" method, the pharmacist should rephrase or repeat the information given (and can also utilize other visual aids to assist relaying the information, if applicable and available). Pharmacists can also offer additional informational resources to patients and/or their caregivers to assist with their health care needs (i.e., Internet or patient-

specific list-serv opportunities, providing health care informational and/or training sessions for groups of patients and providing information/details regarding programs and services offered by other health care providers, government agencies and specialty groups).

There is a pharmacy health literacy assessment tool that is available from the Agency for Healthcare Quality and Research (AHQR) [18] website: http://www.ahrq.gov/qual/pharmlit/pharmlitap3.htm). This pharmacy health literacy tool was designed to measure the perspectives of three critical audiences-objective auditors, pharmacy staff, and patients. The three parts of the assessment are complementary and designed to form a comprehensive assessment. Although, this assessment was designed to be utilized in outpatient pharmacies of large, urban, public health hospitals serving primarily minority populations, it can be utilized by any pharmacy practice setting to assess the setting with regards to health literacy.

Pharmacists have the opportunity to create an atmosphere in their practice that has respect and comfort, which will greatly build trust with patients. When patients are given accurate and important information in a language and format that they can read and understand, they are less reliant on others to assist them in understanding health care issues, they are better able to make informed choices about health care and subsequently they become more empowered and self-reliant with their health care.[19]

So, the next time you dispense a medication that contains a medication information leaflet, think about how you and your colleagues may enhance the delivery of this information to the patient. Do not make the assumption that your patients, regardless of their educational, socioeconomic status, age or gender, are able to understand the written health materials that your setting may be utilizing for patient education. Pharmacists can and should continue to utilize their clinical and professional knowledge to assist patients in understanding important health information.

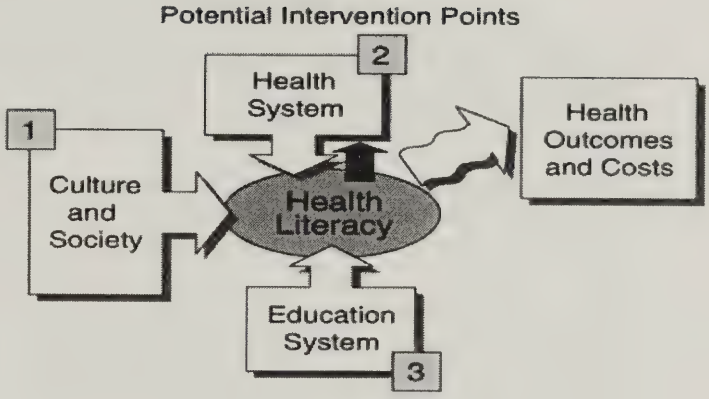



Figure 1: Potential points for intervention in the health literacy framework[1]

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# Continuing Education for Pharmacists

Volume XXV, No. 6

## Schizophrenia and its Therapy: Focus on Paliperidone, a Second-Generation Antipsychotic Drug

**Thomas A. Gossel, R.Ph., Ph.D.**
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**Ohio Northern University**
**Ada, Ohio**

**and**

**J. Richard Wuest, R.Ph., PharmD**
**Professor Emeritus**
**University of Cincinnati**
**Cincinnati, Ohio**

**Goal**. The goal of this lesson is to discuss schizophrenia and its medical management, with focus on paliperidone, a new second-generation antipsychotic drug.

**Objectives**. At the conclusion of this lesson, successful participants should be able to:

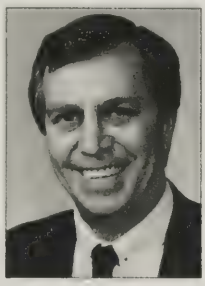
1. describe the pathophysiology, symptoms, and prognosis for schizophrenia;
2. identify the therapeutic considerations for second-generation antipsychotic drugs and differentiate them therapeutically from first-generation drugs; and
3. explain the pharmacologic profile of paliperidone, and advice to convey to patients receiving this medication.

### Background

Schizophrenia is a debilitating mental illness that imposes tremendous personal suffering and impaired functioning, and requires lifelong treatment. Nearly 90 percent of its sufferers are unemployed, and many are dependent on public support or family assistance for their health care and daily living expenses. Between 1994 and 2003, recipients of Social Security disability benefits for schizophrenia increased 35 percent, double the rate of increase of cardiovascular disability and more than three times the growth rate in the U.S. adult population.



Gossel



Wuest

### Schizophrenia

The term *schizophrenia* translates to a *split mind*. Schizophrenia represents a major split between a person's thoughts and actions. Hallmark symptoms include hallucinations and delusions. Impaired information processing is considered the most harmful symptom. Because of its pervasive life impairments and the woeful lack of knowledge regarding its molecular pathophysiology, schizophrenia remains a distressing psychiatric illness.

**Pathophysiology.** The cause of schizophrenia is unknown. Risk factors include both genetic and perinatal considerations with psychosocial stressors serving to precipitate or worsen the factors. The risk for schizophrenia increases in biological relatives of persons with the disease. The risk of disease in first-degree relatives of persons with schizophrenia is 10 percent; when both parents are schizophrenic, the risk in their offspring swells to 40 percent. If one dizygotic (fraternal) twin suffers from schizophrenia, there is a 10 percent chance the other will; and a 40 to 50 percent chance for monozygotic (identical) twins. The lifetime risk is the same for both men and women, but onset is earlier and the outcome poorer in males.

Malnourished women and those who have certain viral infections during pregnancy may be at increased risk of giving birth to children who later develop schizophrenia. Obstetric complications may be associated with an increased incidence of schizophrenia. All of these perinatal risk factors strongly suggest that schizophrenia is a neurodevelopmental disorder, the precise nature of which is not understood.

Studies have demonstrated specific anatomical abnormalities in patients with schizophrenia. Bilateral enlargement of the ventricles within the brain with decreased brain volume has been shown in areas such as the hippocampus and amygdala, although the relationship to schizophrenia remains vague. Abnormalities in the dopaminergic transmission system are theorized to exist in schizophrenic patients, with dopamine overactivity thought to cause the positive symptoms (see below), although such imperfections have never been proven.

**Symptoms.** Symptoms are categorized into three domains. Positive symptoms include those of a psychotic nature such as halluci-

nations, which are usually auditory; delusions; and disorganized speech and behavior. Negative symptoms include decreased emotional range and speech, and loss of interests and self-motivation. Cognitive symptoms include reduced attention span and ability to organize and abstract.

Symptoms normally follow a waxing and waning course but the pattern may change over time. Positive symptoms often respond fairly well to antipsychotic medication, while other symptoms may remain resistant to therapy. Full recovery, especially if the illness has been present for years, is uncommon.

Onset usually occurs in late adolescence or young adulthood. Most deterioration in patients with schizophrenia occurs in the first five to 10 years of onset, and is often followed by decades of relative stability. Although a return to full premorbid functioning is possible, reaching full baseline is unusual. Residual impairment increases with repeated acute episodes; therefore, for many persons, schizophrenia is a lifelong condition.

Schizophrenic patients often display strange and poorly understood behaviors that are rarely noted in normal individuals. These may include prolonged staring at oneself in the mirror, drinking water to the point of intoxication, hoarding worthless objects, experiencing a disturbed wake-sleep cycle, and attempting self-mutilation. Some patients become violent, often resulting from hallucinations or delusions. Violence may result from command hallucinations, e.g., a sense that someone is commanding them to commit a specific task such as murder. Violence is often associated with substance abuse. Treated schizophrenic patients have no greater rate of violence than individuals who do not suffer from schizophrenia. Most schizophrenic patients are not violent, and often fear others rather than being threatening to them.

There are no known pathognomonic (i.e., characteristic that denotes a specific disease) signs or symptoms of schizophrenia. Patients exhibit a variety of symptoms including disorders in thinking, perception, emotional well-being, and interaction with others. Their conversation may be circumstantial (i.e., they take a long time and use much verbiage in answering a question) or tangential (i.e., they never actually answer the question). The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* notes that in order for schizophrenia to be present, a person must experience at least two of the following: hallucinations, delusions, disorganized speech, disorganized or catatonic behavior, or negative symptoms. The patient must also display symptoms for at least one month during a six-month period, along with significant social or occupational deterioration. These problems must not be attributable to any other condition in order for the diagnosis of schizophrenia to be made.

Alcohol and drug abuse are common with up to 70 percent of schizophrenic patients having a comorbid substance abuse problem. Comorbid substance abuse is associated with increased hostility, crime, violence, homelessness, poor nutrition, poverty, and nonadherence with medication instructions.

**Prognosis.** Full recovery is unusual. Early onset of illness, family history of the disease, the presence of comorbid substance abuse, and prominent negative symptoms all suggest a poor prognosis. Patients with schizophrenia have a 10 percent risk of suicide. Nonadherence to medication increases this risk four-fold.

## Medical Management of Psychosis

A goal of therapy is to control symptoms of psychosis to enable individuals to function normally in the community. Antipsychotic therapy is the primary treatment for schizophrenia. The drugs are not a cure. Early diagnosis and treatment of the first episode of schizophrenia may prevent or delay more severe disease. A delay in initiating treatment with antipsychotic medication may increase the need for hospitalization over subsequent years. Unfortunately, the pathologic changes (loss of brain tissue and enlarged ventricles) associated with schizophrenia progress despite treatment with antipsychotic agents.

**Antipsychotic Drugs.** Successful treatments for schizophrenia have been discovered only rather recently. Antipsychotic drugs (neuroleptics; previously referred to as major tranquilizers) have been standard therapy for treating schizophrenia since chlorpromazine (Thorazine) was introduced in the mid-1950s. By 1980, more than 20 other antipsychotic medications were in service. Since clozapine (Clozaril) was shown in the late-1980s to be more effective for treatment-resistant patients with schizophrenia than the older, first-generation agents, numerous second-generation drugs have been synthesized and approved for therapy, each boasting claims of greater efficacy and/or better tolerability than their predecessors. While it is tempting to elaborate further on the many inadequacies of both first- and second-generation antipsychotic agents, it is certainly true that they are far better than pre-1950 approaches.

First-generation ("conventional") antipsychotic drugs are antagonists with high affinity, direct and indirect, complex and simple, for dopamine D2 receptors. They are most effective against psychotic symptoms, but exhibit high rates of neurologic adverse effects, such as extrapyramidal signs (e.g., parkinsonism) and tardive (i.e., late appearing; tardy) dyskinesia. The newer ("atypical" or "novel") agents differ pharmacologically from the older ones in their lessened affinity for dopamine D2 receptors and greater affinities for other

neuroreceptors, including those for serotonin (5-hydroxytryptamine [5-HT] $_{1A, 2A, 2C, 3, 6,}$ and $_{7}$) and norepinephrine ($\alpha_1$ and $\alpha_2$).

Numerous reports indicate that the newer drugs are similar to the conventional ones in reducing psychotic symptoms, and they produce fewer neurologic effects. However, evidence for their superior efficacy has been neither consistent nor robust. An exception is clozapine, which repeatedly has been effective in patients whose condition is refractory to treatment with other agents. But clozapine has a severe adverse effect (agranulocytosis [decreased white blood cells]) that limits its use to treatment-resistant schizophrenia. The newer agents appear more efficacious than conventional drugs in reducing negative symptoms, possibly due to their near-absence of extrapyramidal side effects, or other secondary causes of negative symptoms (e.g., depression) rather than to direct therapeutic effects. The outcomes of studies of effect of treatment on cognitive impairment and mood symptoms have been inconclusive. The ability of the newer agents to prevent relapse, along with their effects on social and vocational functioning, quality of life, long-term outcome, and emotional and physical burden on caregivers, have not been adequately explored.

Nonetheless, many authoritative and widely adopted treatment guidelines for the use of antipsychotics recommend only the newer antipsychotic drugs as first- and second-line treatments, reinforcing the notion that the older drugs are therapeutically inferior. With regard to efficacy, a meta-analysis of treatments published in 2003 found no significant advantage of risperidone (Risperdal), olanzapine (Zyprexa), or quetiapine (Seroquel) over the older drug haloperidol (Haldol). The study did, however, report a lower incidence of extrapyramidal side effects associated with the newer drugs. A separate meta-analysis published the same year of all available studies purporting to examine the differences between second- and first-generation agents demonstrated that the newer agents had both greater efficacy and tolerability over the older ones.

The National Institute of Mental Health sponsored a large randomized controlled trial of over 1400 patients with schizophrenia. The trial (Clinical Antipsychotic Trials of Intervention Effectiveness; CATIE) that started in December 2000 compared the effectiveness of olanzapine, risperidone, quetiapine, and ziprasidone (Geodon) with that of a conventional antipsychotic, perphenazine (Trilafon). Perphenazine was as effective as three of the four newer agents and did not cause more extrapyramidal effects. Olanzapine alone showed marginally greater effectiveness, but was associated with a significantly greater risk of weight gain and other adverse metabolic changes.

**Economic Considerations.** In 1994, the year risperidone was released, annual domestic expenditures on antipsychotic medication totaled $1.4 billion, with fewer than 5 percent of patients receiving the second-generation drugs. A decade later, almost 90 percent of patients with schizophrenia received the newer drugs, with costs exceeding $10 billion annually, 70 percent paid through Medicaid. To this expenditure, the cost of hospitalization and other institutionalized care, the most costly treatment component in human and economic terms, must be considered, which likely more than offsets the direct cost of medication. Overall, the 1990 direct and indirect costs for treatment of schizophrenia were estimated to be $33 billion, accounting for 2.5 percent of U.S. healthcare dollars.

**Adherence to Medication Instructions.** Nonadherence to medication instruction is one of the major problems in treating schizophrenia successfully, and many patients cycle in and out of periods of poor adherence. Schizophrenia is second only to weight reduction in terms of patient nonadherence to treatment instructions for optimizing therapeutic effect. A review showed a mean level of adherence with antipsychotic medication of 58 percent among patients, and research has found that fewer than 25 percent of schizophrenic patients admitted to a hospital were fully adherent. Sixty to 80 percent of patients with schizophrenia discontinued antipsychotic treatment within a few months in one report. Similarly, data from the Veterans Affairs office reveal that about 50 percent of patients with schizophrenia who are discharged from hospitals do not remain on therapy over time. Patients who discontinue medication are almost five times more likely to relapse than patients who continue to take their medication.

It may be assumed that in order for nonadherence to lead to relapse or rehospitalization, the patient has to be medication free for many weeks. An evaluation of 4325 Medicaid outpatients in a western state demonstrated that medication gaps ranging from one to 10 days were associated with an increase in the risk of rehospitalization. The risk of hospitalization increases in direct proportion to the length of the medication gap.

## Paliperidone (Invega)

Invega was approved in December 2006 as an FDA category "1S" drug, meaning that at the time of approval it had not shown significant advantage over currently available treatments. The new drug is the principal active metabolite of risperidone. Its effectiveness in the acute treatment of schizophrenia was established in three six-week, placebo-controlled trials involving 1685 adults in North America, Europe and Asia. In the studies using doses ranging from 3 mg to 15 mg a day, the effectiveness of paliperidone at relieving symptoms of schizophrenia was superior to placebo.

**Mechanism of Action.** The mechanism of action of paliperidone, as with other antipsychotic drugs, is

**Table 1**
**Patient Advice for Invega**

- Tell your doctor if you have ever had an allergic reaction to Invega or Risperdal.
- Take this medicine exactly as prescribed. The usual dose is taken once daily, in the morning. It can be taken with or without food. If you need any information on how to take this medicine, ask your doctor or pharmacist.
- Swallow this medicine whole; do not chew, divide or crush the tablet.
- Use caution when driving or performing tasks that require alertness until you determine how you react to this medicine.
- Other sedating medicines can increase the drowsiness caused by this medicine.
- The manufacturer recommends avoiding consumption of alcoholic beverages while taking this medicine.
- If you develop dizziness or lightheadedness when arising from a seated or lying position, get up slowly. If this continues, tell your doctor.
- Tell your doctor about all other prescription and nonprescription (OTC) medicines, vitamin/mineral supplements, natural products and herbal remedies you are taking.
- If you forget to take a dose, take it as soon as possible unless it is almost time to take your next dose. Do not double your dose unless directed by your doctor.
- Store this medicine at room temperature in a tightly closed container, protected from moisture.
- WOMEN: Notify your doctor if you become pregnant or intend to become pregnant. Do not nurse a child while taking this medicine.

unknown. It has been proposed that the drug's therapeutic activity in schizophrenia is achieved through a combination of central dopamine D2 and serotonin ($5\text{-}HT_{2A}$) receptor antagonism. The drug is also an antagonist at alpha ($\alpha_1$ and $\alpha_2$)-adrenergic receptors and histamine ($H_1$) receptors. It is without affinity for cholinergic muscarinic or beta ($\beta_1$ or $\beta_2$)-adrenergic receptors.

**Adverse Effects and Warnings.** Based on pooled data from the three premarketing studies, adverse events reported with a greater than 2 percent incidence in drug-treated subjects, and increased with dose, included somnolence, orthostatic hypotension, salivary hypersecretion, akathisia (motor restlessness) and Parkinson-like symptoms. The drug's labeling includes the general Boxed Warning that is required of all second-generation antipsychotic drugs of increased mortality in elderly patients with dementia-related psychosis. Other warnings characteristic of first and/or second-generation drugs include QT prolongation; neuroleptic malignant syndrome; tardive dyskinesia; hyperglycemia; and cerebrovascular adverse events including stroke in elderly patients with dementia-related psychosis. Patients with pre-existing severe GI narrowing should not take Invega. The tablets are non-deformable and do not change shape in the GI tract; rare cases of obstruction have been reported.

**Drug Interactions.** Paliperidone has not been shown to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. At therapeutic concentrations, the drug does not inhibit P-glycoprotein; therefore, it is not expected to inhibit P-glycoprotein-mediated transport of other drugs.

Because it produces sedation, paliperidone should be used with caution in combination with other centrally acting drugs and alcohol. It may antagonize the effect of levodopa and other dopaminergic agents. Due to its potential for inducing orthostatic hypotension, an additive effect may be observed when paliperidone is administered with other drugs that have this problem.

**Indications and Uses.** Invega is indicated for the treatment of schizophrenia. Its efficacy has not been evaluated in placebo-controlled trials for longer than six weeks.

**Dosage, Administration, and Availability.** The recommended dose is 6 mg once daily, administered in the morning. Initial dose titration is not required. Doses above 6 mg may provide additional benefit but this must be weighed against the dose-related increase in adverse effects. Some patients may also benefit from a lower dose of 3 mg/day. Dose increases above 6 mg/day should be made only after clinical reassessment and generally should occur only at intervals of more than five days. When an increased dose is indicated, small increments of 3 mg/day are recommended. The maximum recommended dose is 12 mg/day.

Invega can be taken with or without food. Tablets should be swallowed whole with liquids. They should not be chewed, crushed, or divided. The active ingredient is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body. Patients should be advised not to be concerned if they notice something that looks like a tablet in their stool.

Invega is available in extended-release tablets containing 3 mg, 6 mg, and 9 mg paliperidone. Advice to convey to patients is listed in Table 1.

# Continuing Education Quiz

This month's questions are taken from the article on "Schizophrenia and its Therapy: Focus on Paliperidone, a Second-Generation Antipsychotic Drug". Circle your answers to the following questions and mail the entire page to Maryland Pharmacist CE, 650 W. Lombard Street, Baltimore, MD 21201-1572. There is no charge for this quiz for MPhA members (non-members $ 10.00). The completed quiz for this issue must be received by 6/15/10. A continuing education certificate for one and one-half contact hours (0.15 CEUs) will be mailed to you within six to eight weeks. Please type or print clearly. ACPE# 129-144-07-006-H01-P

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**City, State, Zip**_____

**Daytime Phone**_____

**Date Completed** _____
(*Required*)

The Maryland Pharmacy Continuing Education Coordinating Council is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing education for pharmacists.

1. The term *schizophrenia* translates to which of the following?
   a. Scrambled mentality
   b. Senile morbidity
   c. Social menace
   d. Split mind

2. Although it has not been proven, it is theorized that overactivity of which of the following transmission systems causes the positive symptoms of schizophrenia?
   a. Acetylcholine
   b. Dopamine
   c. Gamma-aminobutyric acid
   d. Tryptophan

3. Which of the following symptoms of schizophrenia often responds fairly well to antipsychotic medicines?
   a. Positive
   b. Negative

4. All of the following statements about schizophrenia are true EXCEPT:
   a. alcohol and drug abuse in these patients are common.
   b. patients with schizophrenia have a 10 percent risk of suicide.
   c. full recovery from the disorder is common.
   d. nonadherence to medication increases the risk of suicide four-fold.

5. First-generation antipsychotics exhibit high rates of neurologic adverse effects such as:
   a. blurred vision.
   b. hallucinations.
   c. migraine headaches.
   d. tardive dyskinesia.

6. Which of the following drugs, newer than first-generation, has repeatedly been effective in patients refractory to the other agents?
   a. Quetiapine
   b. Clozapine
   c. Risperidone
   d. Olanzapine

7. Use of the drug referred to in question # 6 is limited due to the following adverse effect.
   a. Agranulocytosis
   b. Antiplatelet action
   c. Aplastic anemia
   d. Eosinophilia

8. Paliperidone is the principal active metabolite of:
   a. clozapine.
   b. olanzapine.
   c. quetiapine.
   d. risperidone.

9. All of the following are correct patient advice for Invega EXCEPT:
   a. place the tablet on your tongue and allow it to dissolve in saliva.
   b. other sedating medicines can increase the drowsiness caused by this medicine.
   c. avoid alcoholic beverages while taking this medicine.
   d. if you develop dizziness or lightheadedness when arising from a seated or lying position, get up slowly.

10. It has been proposed that paliperidone is without affinity for which of the following receptors?
   a. Alpha-adrenergic
   b. Cholinergic
   c. Histamine
   d. Serotonin

**Please note: The ACPE Number for "Challenges in Pharmacy Practice: Dispensing Errors and Their Prevention that was in April/May/June 2008 Journal was incorrect. The correct ACPE Number is 129-144-08-001-H05-P.**

# Medication Therapy Management: A Review of the Core Elements, Perceptions, and Opportunities for Pharmacists

Kristen M. Fink, PharmD, CDE; Hoai-An Truong, PharmD, MPH; Kristen Malone, PharmD Candidate

*The **MPhA Professional Development Committee**, in an effort to increase awareness and promote opportunities for Medication Therapy Management (MTM) services in Maryland, presents this first article summarizing the core elements of an MTM service model and perceptions of provider, payer, and patient. A second article in the next "Maryland Pharmacist" will focus on opportunities, including national and state initiatives and resources for pharmacists to provide MTM.*

MTM services are an expansion from the philosophy and process of pharmaceutical care in pharmacy practice, in which pharmacists are recognized as "medication therapy experts" who provide "patient-centered" care. Recognizing the pharmacist's evolving role, a consensus conference of eleven national pharmacy organizations defined MTM services as "a distinct service or group of services that optimize therapeutic outcomes for individual patients. MTM services are independent of, but can occur in conjunction with, the provision of a medication product. MTM has a broad range of professional activities and responsibilities within the licensed pharmacist's…scope of practice… according to patient's individual needs."[1]

The American Pharmacists Association and the National Association of Chain Drug Stores Foundation, along with an advisory panel of pharmacy practice leaders, developed a model framework for MTM. This MTM service model, which includes five core elements that pharmacists can integrate into MTM services within their pharmacy practice, is distinct from the medication dispensing process. These five core elements are consistent with the Centers for Medicare and Medicaid Services (CMS) expectation that "MTM service will enhance patients' understanding of the appropriate drug use, increase compliance with medication therapy, result in collaboration between pharmacists and prescribers, and improve detection of adverse events."[1]

- **Medication Therapy Review (MTR)**

A systematic process of collecting patient-specific information, assessing medication therapies to identify medication-related problems, developing a prioritized list of medication-related problems, and creating a plan to resolve them.

- **Personal Medication Record (PMR)**

A comprehensive record of the patient's medications, including non-prescription medications, herbal products, and other dietary supplements.

- **Medication-related Action Plan (MAP)**

A patient-centric document containing a list of actions for the patient to use in tracking progress for self-management.

- **Intervention and/or Referral**

Pharmacist provides consultative services and intervenes to address medication-related problems; when necessary, the pharmacist refers the patient to physician or other health care professional.

- **Documentation and Follow-up**

MTM services are documented in a consistent manner; and a follow-up visit is scheduled based on the patient's medication-related needs, or the patient is transitioned from one care setting to another.

Medication-related problems are a significant public health concern with an estimated 1.5 million preventable medication-related adverse events occurring each year in the United States. MTM may contribute to the prevention of these errors and help patients to become actively involved in their own health care. Any patient who uses a prescription, non-prescription, herbal or dietary supplement could potentially benefit from a medication therapy review (MTR). It is also important to realize that MTM, although often associated with the Medicare population, can benefit patients of all ages in all settings. Patients who experience changes in primary providers or health care settings often have an increased risk for medication-related problems. As the most accessible health care professional, pharmacists have the unique opportunity to provide MTM services and ensure continuity of patient care. Patients with the potential need for MTM services can be identified by the pharmacist, provider, health plan or the patient themselves.

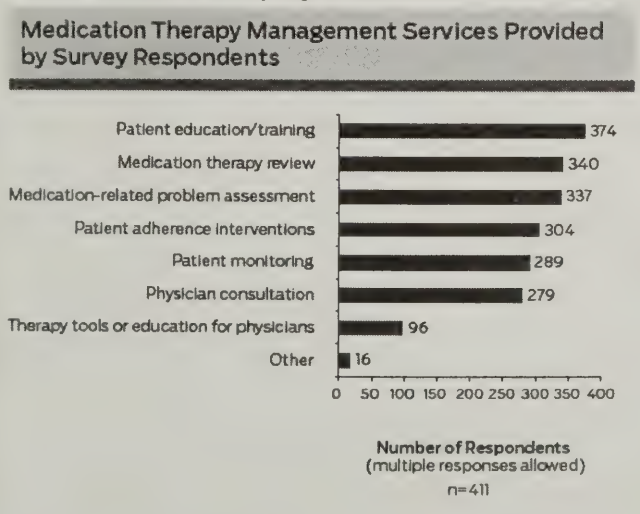
The American Pharmacists Association, under the direction of an independent advisory board, conducted two surveys to evaluate strategies for MTM service implementation and the value of these services to

providers, payers and patients. The full summary of findings, titled "MTM Digest," can be found on the APhA website. There were 687 pharmacist providers, with the largest representation from independent pharmacy respondents. Sixty-three percent of respondents were already providing MTM services, citing numerous reasons why they were motivated to implement these services. Reasons ranged from meeting patient needs and professional satisfaction to having the opportunity to increase business and revenue sources.

Twenty-six payers responding to the survey reported offering an MTM service benefit to their members. The majority of these payers recognized pharmacists as the most qualified provider of these services because of their training, expertise, availability and cost. Seven payers gave specific payment information. Five reported having a fee-for-service contract with providers either on a per encounter basis or per minute flat fee. Payments per encounter ranged from $20 for a follow-up visit to flat payments of $90.50 per encounter. Payers reported per minute flat fees of $2 per minute, and pharmacist respondents reported fees ranging from $1 to $3 per minute. Payers reported a positive impact on their quality measures and organization needs, including reductions in overall health care costs, adverse events, hospitalizations, emergency room visits and prescription costs. The median return on investment calculated by payers for MTM services was 3:1.[1]

### Services Provided

**Survey respondents providing medication therapy management reported performing a variety of associated activities for a diverse array of patients.**




Source: APhA MTM Digest: Prespectives on MTM Service Implementation

**Factors Influencing the Decision to Implement Services**

| Reasons to Implement (n = 381) | |
|---|---|
| 1. Patient needs | Most Important ▲ |
| 2. Responsibility as health care provider | |
| 3. Recognized need to improve health care quality | |
| 4. Contribution to health care team | |
| 5. Professional satisfaction | |
| 6. Reducing health care system costs | |
| 7. Primary business mission | |
| 8. Reducing health insurer costs | |
| 9. Provider needs | |
| 10. Need for other revenue sources | ▼ |
| 11. Competitive pressure | Least Important |
| 12. Decreased prescription volume | |

Source: APhA MTM Digest: Prespectives on MTM Service Implementation

The most frequently reported barrier to implementing MTM services was patients' lack of perception of need. Generally, patients had a favorable opinion of pharmacists providing MTM services; and those who had previous exposure to pharmacist-provided services recognized the importance of these services. The survey concluded that "increasing patient awareness about MTM may increase their appreciation of, and desire for, these services."[1]

Numerous opportunities exist for pharmacists who want to provide MTM services. As medication experts, pharmacists have the knowledge and expertise to improve patient's medication use, clinical outcomes, and overall health care. As more information is disseminated amongst providers, payers and patients, MTM services have the potential to become one of the fastest growing segments of pharmacy professional services.

Acknowledgement:

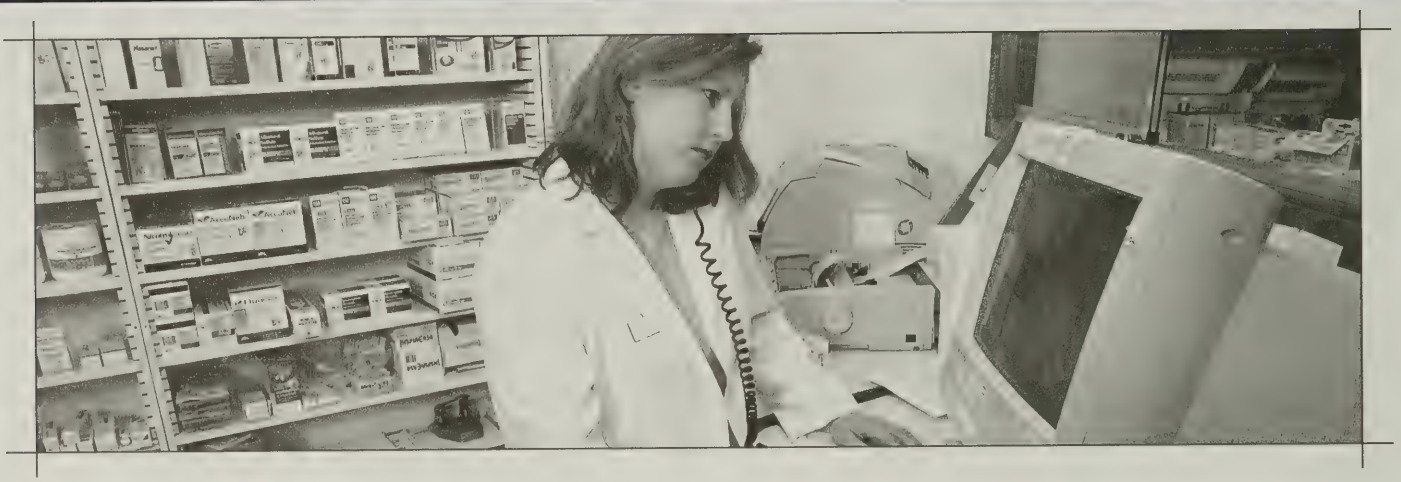
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1. American Pharmacists Association. *MTM Digest: Perspectives on MTM Service Implementation.* March 2008 Available at: www.pharmacists.com/mtm.
2. American Pharmacists Association and National Association of Chain Drug Stores Foundation. MTM in Pharmacy Practice: *Core Elements of an MTM Service Model.* Version 2.0; March 2008.

*For questions regarding MTM opportunities, please contact* ***MPhA Professional Development Committee*** *co-chairs Kristen M. Fink, Clinical Pharmacy Specialist II, Kaiser Permanente at fink462@hotmail.com, or Hoai-An Truong, Assistant Director of Experiential Learning Program, University of Maryland School of Pharmacy at htruong@rx.umaryland.edu.*

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Happy Holidays!

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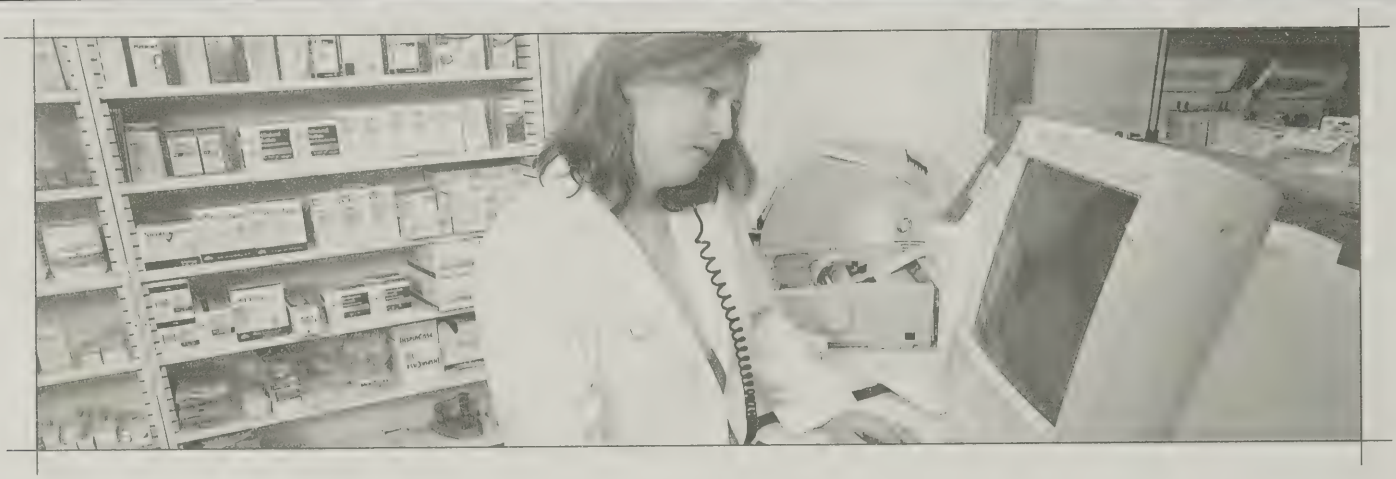

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# Presidents' Message:

## MPhA is on the MOVE!! Empowering Pharmacists to Act Now: Seize the time and the Opportunities!!



Magaly Rodreguez de Bittner, Pharm.D.
President

*Colleagues, I believe that is critical for MPhA to continue to provide pharmacists with the resources they need not only to do their jobs but also to create new opportunities for the profession. In the past two years, we have been instrumental in providing leadership with collaborative practice, the Maryland P3 program, MTM training, CE at the midyear and annual meetings, immunizations and PBM bills just to mention a few.*

*MPhA has emerged as a leader and a resource for our pharmacists. This work must continue and expand; we must empower pharmacists to take responsibility to define their profession—not to allow others to define it. We must act now to define our future!*

To illustrate this point, I would like to tell you a story I heard from a Texas Senator who also happens to be a pharmacist. She related the story of her grandmother who lived in Texas but had to cross the border to work in Mexico with a rich family. Every time she crossed the border back into the US (even though she was a US citizen) she was asked the following questions by the border patrol agent:

1. **Who are you?** – If you were asked, "who are you, pharmacist"? Would you be able to answer the question? Are you a community pharmacist, hospital pharmacist, long term care pharmacist, consultant, academician? Could you articulate with a unified voice who a pharmacist is? A medication expert, a member of the health care team, a leader in the community, a patient advocate or a health care "coach"?

2. **What do you bring?** – What are the sets of skills that we bring to the health team? Can you articulate a collective set of skills that we bring to the table? What solutions do we bring to the health care issues we are experiencing in Maryland and the US? Could we articulate with a common vision what we bring? Medication expertise, accessibility of care, unique knowledge and skills on solving medication related issues?

3. **Where are you going?** – Where are we going as pharmacists? Do we know our destination? Can we collectively articulate where we are going? Are we in agreement of what our destiny or future should be? Is our vision to be an active and respected member of the health care team, to gain recognition and payment by payers for our value in patient care and health outcomes, or to gain the public recognition of our role in health care? Do we have a common destination? Have we clearly articulated to others our destination?

4. **What are you going to do when you get there?** – What are your plans when you get there? Can you clearly articulate the professions' vision of what you are going to do when you get to your destination or what we are going to do when the opportunities we have been asking for become a reality? Do we have a clear definition of our tasks and responsibilities? Do we have a common understanding of our role as health care providers and our responsibility for patient outcomes?

As you can see, there is need for us to have a more active discussion of our destiny and to clearly articulate where we want to go. For this reason, in the next few months, your association will engage in a strategic planning process to gain an appreciation of where the pharmacy profession in Maryland wants to go and to develop concrete goals to achieve it. We will be calling on you to share with us the answers to the questions discussed above.

MPhA is on the Move to Empower Pharmacists in Maryland!



# Recognizing Pharmacy Excellence
# The 2009 MPhA Awards

Each year, the Maryland Pharmacists Association recognizes professional excellence through a series of awards. To nominate a pharmacist for one of the awards described below, complete the Official Award Nomination Form. The forms should be submitted to: Award Nominations, c/o Maryland Pharmacists Association, 650 West Lombard Street, Baltimore, Maryland 21201-1572.

All nominations will be reviewed by the Past Presidents Council who is responsible for selecting the award recipients. The decision of the Council is final. Award recipients will be notified in advance of the award's presentation at the Annual MPhA Convention.

For consideration, all nominations must be received no later than ***Friday, Febuary 27, 2009.***

- **Pharmacists Mutual Distinguished Young Pharmacist Award**
  Awarded to a pharmacist who graduated within the past ten years and has made a significant contribution to the profession through service to a local, state or national pharmacy organization. ***Who is Eligible:*** Any MPhA pharmacist member who graduated from pharmacy school in 1999 or after.

- **Maryland Pharmacists Association Honorary President**
  An honorary position on the Board of Trustees given to a person, not necessarily a pharmacist, who has worked for the MPhA or Maryland Pharmacy over a long period of time. ***Who is Eligible:*** Any long standing contributor to the profession or the Association.

- **MPhA Mentor Award**
  This award recognizes individuals who encourage pharmacists, technicians, and/or student pharmacists in the pursuit of excellence in education, pharmacy practice, service, and/or advocacy. ***Who is Eligible:*** Any MPhA pharmacist member who meets the criteria of the Award.

- **Seidman Distinguished Achievement Award**
  Created to honor the major impact on the pharmacy profession by Henry Seidman, this award is presented for outstanding service by a Maryland pharmacist to the pharmacy profession during *either* the past year or over a period of years. ***Who is Eligible:*** Any MPhA pharmacist member who meets the criteria of the award.

- **Wyeth-Ayerst Bowl of Hygeia Award**
  The Bowl of Hygeia recognizes a pharmacist who has performed outstanding services to the community in any area, with a particular emphasis on non-pharmacy contributions. ***Who is Eligible:*** Any MPhA member pharmacist who has not already received the Bowl of Hygeia.

- **Innovative Practice Award**
  Established in 1993, this award aims to recognize forward-thinking pharmacists who have expanded their practices into new areas. Any practicing pharmacist member within the geographic area who has demonstrated innovative pharmacy practice resulting in improved patient care. ***Who is Eligible:*** Any MPhA pharmacist member who meets the criteria of the award.

# Maryland Pharmacists Association
# Award Nomination Form

To nominate a Maryland pharmacist for one of MPhA's annual "Recognizing Pharmacy Excellence" awards, this form must be completed and returned to the Maryland Pharmacists Association no later than ***Friday, February 27, 2009***. All nominations will be held in strictest confidence by the MPhA Past Presidents Council, which is responsible for selecting the award recipients. The decision of the Council is final. Award recipients will be notified in advance of the presentation of the award.

Please consider the following nominee for:

☐ ***Pharmacist Mutual Distinguished Young Pharmacist Award***
Nominee _____
Address _____
City, State & Zip _____
Daytime Phone _____
Employment/Practice _____
Nominated by _____ Nominator's Phone _____

☐ ***Seidman Distinguished Achievement Award***
Nominee _____
Address _____
City, State & Zip _____
Daytime Phone _____
Employment/Practice _____
Nominated by _____ Nominator's Phone _____

☐ ***Innovative Practice Award***
Nominee _____
Address _____
City, State & Zip _____
Daytime Phone _____
Employment/Practice _____
Nominated by _____ Nominator's Phone _____

☐ ***Wyeth-Ayerst Bowl of Hygeia***
Nominee _____
Address _____
City, State & Zip _____
Daytime Phone _____
Employment/Practice _____
Nominated by _____ Nominator's Phone _____

☐ ***MPhA Mentor Award***
Nominee _____
Address _____
City, State & Zip _____
Daytime Phone _____
Employment/Practice _____
Nominated by _____ Nominator's Phone _____

☐ ***MPhA Honorary President***
Nominee _____
Address _____
City, State & Zip _____
Daytime Phone _____
Employment/Practice _____
Nominated by _____ Nominator's Phone _____

Attach a current resume or curriculum vitae for the nominee that shows their professional and personal achievements. This information is essential for the Past Presidents Council to make its decisions as to which candidates will be recipients of the "Recognizing Pharmacy Excellence" awards. In addition, the nominator should attach a brief letter explaining why the nominee is worthy of receiving this award.

Return the completed form to:

**Awards Nominations**
c/o Maryland Pharmacists Association
650 W. Lombard Street
Baltimore, MD 21201-1572

Fold

**2009 Awards Nominations**
Maryland Pharmacists Association
650 W. Lombard Street
Baltimore, MD 21201-1572

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# "Therapeutically Speaking..."

## Optimizing Effective Pharmacotherapy Conversations Using the SBAR Method

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*Who was it that said, "What we have here is a failure to communicate"? To put you out of your misery—we'll tell you—Paul Newman in Cool Hand Luke (http://ask.yahoo.com/20011026.html). We know that ineffective verbal and written communication between health care providers is not only annoying, but can result in suboptimal health outcomes. Let's look at an example. You're hard at work in your community pharmacy, slaving away, phones ringing, 37 patients in line, and the technician calls back, "Line 3 is for you." You pick up the phone to be greeted by a nurse in one of the assisted living facilities your pharmacy provides medications for.*

*"I really need some help," she says. "I'm really sorry to bother you so early on a Monday morning."*

*"No problem," you respond. "What can I do for you?"*

*"Well, Mrs. Johnson is having a lot of chest pain. Do you think it's that new medication we started that you sent out on Thursday?"*

*Okay, can I buy a vowel? Phone a friend? Who is Mrs. Johnson? How old is she, what's wrong with her, and what new medicine are you talking about? Curbside consults that start out like this frequently end up feeling like a game of twenty questions!*

The Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) reports that 65% of sentinel events, and 90% of root cause analyses conducted at a hospital in Illinois include poor communication as a contributing factor.[1] Effective communication is so important that JCAHO implemented a patient safety goal effective January 1, 2006 that states "facilities must implement a standardized approach to hand-off communications, including an opportunity to ask and respond to questions." The need to succinctly and accurately convey information between health care providers affects pharmacists on both the receiving end (as above) and when providing information to another health care provider.

In an effort to structure communication to help clinicians have a shared mental model for a patient's clinical condition, Dr. Michael Leonard, a physician leader for patient safety at Kaiser Permanente in Denver introduced the "SBAR" model. "SBAR" stands for Situation, Background, Assessment, and Recommendation. Let's take a look at each of these elements.

Situation – a brief statement of the problem; what is happening at the present time that has warranted the SBAR communication. It's important to identify yourself, your title, your practice (pharmacy), the patient's name (and probably include patient's age and primary diagnosis), and a very brief (one-liner) statement of why you are calling. "Hello Nurse Practitioner Evans. This is Jane Doe, the pharmacist from ABC Pharmacy. I'm calling about Nancy Jones, a 28 year old female for whom you called in a prescription for ciprofloxacin a few hours ago."

Background – explain the circumstances that lead up to this situation. This is important to put the situation into context for the listener. You may need to include pertinent medical history, and clinical information (current medications, allergies, vital signs, symptom assessment) to paint a succinct, yet complete picture of the situation. "You may not even be aware of this, but Ms. Jones is approximately 2 months pregnant. Her obstetrician called in an order for prenatal vitamins about 2 weeks ago. Ms. Jones is here in the pharmacy now, and asking for her antibiotic for the urinary tract infection she discussed with you."

Assessment – you provide an analysis of the situation, and what you have found, or think is going on. It is also perfectly acceptable to describe a clinical situation and your assessment may be "I have no idea what's going on." Continuing with Ms. Jones, "As you know, ciprofloxacin is pregnancy category C due to concerns of cartilage damage in animal models. Because of this ciprofloxacin should only be used during pregnancy if a safer option is not available. I think there are better options available."

Recommendation – this is where you recommend what action you could like to occur. Frequently pharmacists forget this step, and just ask "so what do you want to do?" If you have a sound recommendation,

make it – otherwise you may have to deal with an off-base recommendation! To wrap up with Ms. Jones, you finish by saying, "In terms of antibiotic selection, ampicillin has historically been the drug of choice for a UTI in pregnancy, but we're seeing a significant amount of resistance. Nitrofurantoin is a good choice because you achieve high urine concentrations. Cephalosporins are acceptable and well-tolerated. Even a sulfonamide is acceptable in the first or second trimesters, but not in the third trimester because it's thought to increase the risk of kernicterus in the fetus, especially a preterm infant. If a urine specimen for culture and sensitivity was done, do you want me to hold while you pull the lab results so we can settle on a new antibiotic for Ms. Jones?"

Let's look at another example – this time the pharmacist is providing MTM services in a patient with diabetes, dyslipidemia, hypertension, and pain management. The pharmacist is working with Mr. Smith today. Let's listen in as the pharmacist contacts Mr. Smith's primary care physician with a recommendation:

Situation – "Hello Dr. Hill. This is Don Johnson, the pharmacist at Johnson Drugs. I've been working with your patient Sam Smith, a 72 year old man with diabetes who is complaining of increased pain in his feet."

Background – "Mr. Smith has an 18 year history of type 2 diabetes, and a history of depression and hypertension. His diabetes is being treated with sitagliptin, metformin and glyburide. He is complaining again today of pain in both feet on the bottoms and the tops, which has been going on for several months now. He complains of numbness and tingling in his feet, with occasional burning. He says the pain is worse at night, but nothing in particular brings it on. I inspected his feet, and he shows decreased sensation to monofilament testing, ankle and knee jerks and decreased two point discrimination and vibratory sensation. He rates the pain as a best of 4 (on a 0 = no pain; 10 = worst imaginable pain scale), a worst of 8 and an average of 6. The pain prevents him from getting a good night's rest. On his last visit to the pharmacy he wanted to try ibuprofen, and unsurprisingly, this did not reduce the pain. He has tried ice packs and a heating pad as well with no relief."

Assessment – "I believe Mr. Smith is experiencing painful diabetic neuropathy in both feet."

Recommendation – "I recommend Mr. Smith discontinue the nonprescription ibuprofen, and we should begin an agent shown to be effective in treating painful diabetic neuropathy. He tells me he would welcome treatment for his depression, so I recommend we begin duloxetine 20 mg once daily (Cymbalta) which will likely be beneficial for both the depression and neuropathic pain. We can titrate the duloxetine to 60 mg over the next week or two. What do you think of this plan?"

Wow – Pharmacist Johnson is a rock star! This is a good example of a succinct, yet comprehensive clinical encounter with another clinician. The pharmacist described the situation and background, and provided an assessment and plan. You might notice that in the background, Pharmacist Johnson provided a very careful, yet inclusive description of the patient's pain. He followed the "PQRSTU" model of symptom analysis. Any symptom a patient complains of can be more fully described with this model. What does PQRSTU stand for? Take a look:

P – precipitating, palliating, previous treatment of therapy: What brings the symptom on or makes it worse; what alleviates the pain, and have you tried any medication to treat the symptom? If so, how well did it work and did you have any adverse effects?

Q – quality: Please describe the how the symptom (pain) feels in your own words.

R – radiation: In the case of pain, does the pain travel anywhere else? Are you experiencing symptoms anywhere else?

S – severity: Please tell me how severe the symptom is. In the case of pain, we use the 0-10 scale, and ask about the worst rating during the day, the best, and the average.

T – temporal: How long have you have this complaint? Is it constant or intermittent? How many times per day do you experience this symptom? How long does it last when it occurs?

U – YOU: How does this symptom affect your quality of life. For example, you could ask, "What would you like to be able to do that you can't do now because of the pain." Typical answers include "sleep through the night, go back to work, do my grocery shopping," etc.

Whether you're on the receiving or providing end of a clinical encounter, effective communication makes all the difference in the world. Quickly gathering and jotting down your thoughts before picking up the phone will enhance your ability to provide accurate information, improve your credibility, and most important, lead to optimal patient care! Remember, SBAR rocks!

**PHARMACY MARKETING GROUP, INC**



# AND THE LAW

By Don R. McGuire Jr., R.Ph., J.D.

***This series, Pharmacy and the Law, is presented by Pharmacists Mutual Insurance Company and your State Pharmacy Association through Pharmacy Marketing Group, Inc., a company dedicated to providing quality products and services to the pharmacy community.***

## NEGLIGENCE 101

In the past, this series has examined a number of legal and claims issues. Think back to your pharmacy law class in college. How much do you remember about the elements of negligence? What does a plaintiff have to prove in order to win a negligence case? Time for Negligence 101 class to begin.

The more common types of claims involving pharmacists are negligence claims. Negligence is one category of cases in the area of the law known as Torts. Negligence is defined as "the failure to exercise that degree of care which a person of ordinary prudence would exercise under the same circumstances."[1] As you might have guessed, negligence and neglect derive from the same root word. Negligence does not include reckless behavior or intentional behavior.

To win a negligence case, the plaintiff must prove four elements. They are: duty, breach of that duty, proximate cause, and harm. We will examine each of these elements in turn as they apply to pharmacy practice.

Duty is the requirement to behave in a certain manner for the benefit of another. Pharmacists do have certain duties to their patients. There is a long line of cases that indicate that a pharmacist has a duty to fill a patient's prescription correctly. Previous to changes in pharmacy practice, this was the pharmacist's only duty to their patients. Today, we have additional duties, such as patient counseling and drug regimen reviews. The courts in the various states have been slow to recognize these additions to the pharmacists' duties. This results in differing case law from state to state. However, the pharmacist's duties to their patients are not unlimited. The pharmacist has to take only reasonable steps to prevent foreseeable harm. Therefore, it is not required to prevent all harm. If the plaintiff's case involves a situation where the pharmacist did not have a duty to the plaintiff, then the case will fail.

The second element of a negligence case is whether a breach of the pharmacist's duty to the patient has occurred. A duty can be breached in one of two ways. The required duty is not performed (nonfeasance) or the activity is performed, but it is incomplete or incorrectly done (malfeasance). This element most likely will require some proof of the standard of care. This involves the testimony of expert witnesses.

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1 Barron's Law Dictionary, Second Edition, Barron's Educational Series, Inc., 1984.

The expert witness will draw on their own experience, laws and regulations, codes of ethics, and other such items to determine if the pharmacist performed their required duties adequately. In cases where a prescription has been misfilled, this element is not hard to prove. Case law is full of cases that state that a pharmacist must fill prescriptions correctly. If you don't, that is a breach of duty. However, in cases where it is alleged that the pharmacist failed to perform DUR or provide patient counseling, it can be more difficult. Many times you will have opposing testimony from experts, as well as from opposing testimony from parties. It is usually not clear-cut what the judge or the jury will decide when they are given conflicting testimony.

The third element that the patient must prove in order to prevail is that they were injured or harmed. In many cases, this is not too difficult. The patient became dizzy and fell, their blood sugar dropped precipitously, their blood pressure increases or decreases, or they suffered an allergic reaction. Many states require a physical injury in order to make a claim for emotional injuries. The theory here is that claims for anxiety, stress, sleeplessness, etc. are more credible if they result from a bodily injury. Sometimes it is difficult to separate the symptoms complained of from the patient's underlying pre-existing conditions. This leads us to the fourth element.

The injury that the patient suffered must have been proximately caused by the breach of duty. That is, if a prescription is misfilled, the injury suffered must be due to the misfill and not some other cause or underlying condition. For example, a person who experiences high blood pressure after taking an overdose of an antihypertensive drug would cause you to question if the misfill actually caused those symptoms. This element becomes very important in cases where it is not clear if the patient actually took the drug in question, or that the symptoms could be caused by some other factor. Again, this is an area where the use of expert witnesses is very important. There is also another concept under this element. It is called superceding or interceding cause. Suppose that a patient had been taking the wrong medication for a couple of days when she is involved in a car accident. The impact breaks her leg and requires surgery to repair the bone. Obviously, this injury is not the result of the misfill and would not be proximately caused by it. This injury would not be compensable under the misfill claim.

In summary, for a patient to prevail in a negligence claim against a pharmacist, the patient must prove the four elements of negligence. They are duty, breach of that duty, proximate cause, and harm. If they fail to prove even one of the elements, then there will be no monetary damages awarded to them. However, in cases involving the misfiling of potent medications, such as methotrexate or warfarin, this burden of proof is not a huge obstacle to overcome.

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© Don R. McGuire Jr., R.Ph., J.D., is General Counsel at Pharmacists Mutual Insurance Company.

*This article discusses general principles of law and risk management. It is not intended as legal advice. Pharmacists should consult their own attorneys and insurance companies for specific advice. Pharmacists should be familiar with policies and procedures of their employers and insurance companies, and act accordingly.*

# Continuing Education for Pharmacists

Volume XXV, No. 9

## Women's Health: Breast Cancer and its Treatment: Focus on Lapatinib (Tykerb)

**Thomas A. Gossel, R.Ph., Ph.D.**
**Professor Emeritus**
**Ohio Northern University**
**Ada, Ohio**

**and**

**J. Richard Wuest, R.Ph., PharmD**
**Professor Emeritus**
**University of Cincinnati**
**Cincinnati, Ohio**

**Goal.** The goal of this lesson is to discuss breast cancer and its medical management with focus on lapatinib, a new targeted therapy for breast cancer.

**Objectives**. At the conclusion of this lesson, successful participants should be able to:

1. demonstrate knowledge of the pathophysiology, risk factors, symptoms, detection, and prognosis for breast cancer;
2. exhibit an understanding of the therapeutics of lapatinib including its pharmacologic and toxicologic profile, along with the role of targeted therapy for breast cancer; and
3. select examples of information to convey to patients on Tykerb therapy.

An estimated 178,480 new cases of invasive breast cancer are expected to occur among women in the United States during 2007. Breast cancer is the most frequently diagnosed cancer in women. Metastatic breast cancer is the leading cause of death from cancer among women around the globe, accounting for more than 400,000 deaths each year.



Gossel



Wuest

***Signs and Symptoms***. The earliest sign of breast cancer is most commonly an abnormality – a lump or mass – detected within the breast on a mammogram. Larger tumors may become noticeable as a painless mass. Other (less common) symptoms include changes to the breast such as distortion, scaliness, skin irritation, swelling, tenderness or thickening, or abnormalities to the nipple such as retraction, a spontaneous discharge other than breast milk, or ulceration. Breast pain from benign conditions is typically not an early symptom of breast cancer. Stromal invasion and metastasis to regional lymph nodes or distant organs are the hallmarks of fully developed breast carcinomas.

Most patients with breast cancer have disease localized to the breast and axillary (armpit) lymph nodes. Approximately half of the patients initially diagnosed with early breast cancer may develop metastatic disease.The most common sites of metastatic disease are bone, liver, lungs, skin, and brain.

***Risk Factors***. Age is the most important factor associated with development of breast cancer in women. Breast cancer is rare in women under 30 years of age; half of all breast cancers are diagnosed in women older than 60 years of age. Risk is also increased by high breast tissue density, hyperplasia (especially atypical hyperplasia), following a large dose of radiation to the chest as a result of medical procedures, by inherited genetic mutations in the BRCA1 and BRCA2 genes, and a family history of breast cancer. Having a first-degree relative (mother, sister, or daughter) with breast cancer increases a woman's risk, while having more than one first-degree relative who has or had breast cancer before the age of 40, or in both breasts, increases a woman's risk even more. Most women with breast cancer, however, do not have a first-degree relative with the disease. Reproductive factors, including a long history of menstrual periods (starting early and/or ending late in life), never having children or having the first child after age 30, and recent use of oral contraceptives increase the risk.

Other factors that increase the risk include being overweight or obese following menopause, use of postmenopausal hormone therapy (especially combined estrogen/progestin therapy), physical inactivity, and consumption of one or more alcoholic beverages every day.

In contrast, risk is lowered by breastfeeding, moderate to vigorous physical activity, and maintaining a healthy body weight. Tamoxifen (Nolvadex, etc.) decreases breast cancer risk in women known to be at increased risk. Raloxifene

**Table 1**
**Screening Guidelines for Early Detection of Breast Cancer in Asymptomatic Women**

- Yearly mammograms are recommended starting at age 40.
- Clinical breast examination (as part of a periodic health examination) about every 3 years for women in their 20s and 30s, and every year for women 40 and older.
- Women should know how their breasts normally feel and report any change promptly to their physician. Breast self-exam is an option for women starting in their 20s.
- Women at increased risk (e.g., family history, genetic tendency, past breast cancer) should discuss with their physician about the benefits and limitations of starting mammography screening earlier, having additional tests (i.e., breast ultrasound and MRI), or having more frequent examinations.

(Evista) is as effective as tamoxifen in reducing the risk of invasive breast cancer in post-menopausal women, but is not approved for this purpose. Mutations in the BRCA1 and BRCA2 genes account for approximately 5 to 10 percent of all breast cancer cases; however, widespread testing for these mutations is not recommended at this time since they are present in less than 1 percent of women in the general population. Women with a strong family history of breast cancer may be counseled to determine if genetic testing is appropriate. Prophylactic removal of the breasts in BRCA1 and BRCA2 mutation carriers decreases the risk considerably.

***Detection***. The earlier breast cancer is discovered, the better the chance for successful treatment, thus enhancing the survival rate. A mammogram is currently the best method to detect cancers because it can often identify breast abnormalities that may be cancerous before symptoms appear. Guidelines for early detection of breast cancer in asymptomatic women are presented in Table 1.

Magnetic resonance imaging (MRI) is more sensitive than mammography in detecting tumors in women. However, MRI leads to more false-positive results than mammography. Such false-positive outcomes can lead to a high number of otherwise avoidable biopsies, thus creating unnecessary fear, anxiety, and other adverse health effects. It is important to carefully select those women who should be screened using this technology.

For women at high risk, the American Cancer Society recommends MRI and mammograms at age 30 unless otherwise determined by their physician. The 2007 guideline recommends MRI screening in addition to mammography for women who meet at least one of the following conditions:

- a BRCA1 or BRCA2 mutation;
- a first-degree relative with a BRCA1 or BRCA2 mutation, even if they have yet to be tested themselves;
- their lifetime risk of breast cancer is determined to be 20 to 25 percent or greater;
- they received radiation therapy to the chest between 10 and 30 years of age; and
- they have Li-Fraumeni syndrome, Cowden syndrome, or Bannayan-Riley-Ruvalcaba syndrome, or have one of these syndromes in first-degree relatives.

***Treatment***. Treatment may involve lumpectomy (surgical removal of the tumor with clear margins) or mastectomy (surgical removal of the entire breast) with removal of some axillary lymph nodes. It may also involve chemotherapy, radiation therapy, hormone therapy (tamoxifen; aromatase inhibitors, e.g., anastrozole/Arimidex, letrozole/Femara), or targeted biologic therapy, described subsequently. Trastuzumab (Herceptin) is a humanized monoclonal antibody that binds to the extracellular domain of the HER2 protein, a key component in the treatment of metastatic and early-stage HER2-positive breast cancer. Optimal management of breast cancer remains a significant therapeutic challenge, and multiple therapies are often used. Unless cancer has spread to the skin, chest wall, or distant organs, many studies have confirmed that long-term survival following lumpectomy plus radiation therapy is comparable to survival rates following mastectomy, and this procedure has replaced mastectomy as the preferred surgical approach for treating women with early stage breast cancer.

The percentage of DCIS (ductal carcinoma in situ) that would advance to invasive breast cancer without treatment is not known. Data from mammography screening trials suggest that the majority of such tumors will progress, and all patients with DCIS should be treated. Treatment options include lumpectomy with radiation therapy, or mastectomy. Either procedure may be followed with tamoxifen.

Current treatment goals for management of metastatic or advanced breast cancer include a delay in disease progression, prolongation of survival, amelioration of symptoms, and optimizing quality of life. Several factors influence the decision regarding treatment choices for metastatic cancer and include the patient's overall condition (e.g., presence of comorbidities), sites of metastases, previous treatment regimens, and biologic characteristics of the tumor. In addition, treatment of specific complications localized to selective tissues is now used routinely. Bisphosphonates (e.g., alendronate/Fosamax, ibandronate/Boniva, risedronate/Actonel) for example, can be used to reduce bone pain and other skeletal events in women with advanced breast cancer.

***Targeted Therapy***. Traditional cancer therapies (i.e., chemotherapeutics) have historically been developed without identification of a tumor-specific molecular profile that would predict their response. Patients were, therefore, at high risk of a wide variety of adverse effects from relatively non-specific

(non-targeted) treatments that may provide only limited therapeutic benefit. Recent advances in oncology have provided greater understanding of the biologic processes that regulate tumor cell growth, including their chemical characteristics, leading to the development of targeted cancer therapy.

The tyrosine kinase inhibitors (e.g., imatinib/Gleevec, erlotinib/Tarceva, gefitinib/Iressa), and more recently lapatinib (Tykerb) represent a class of targeted cancer drugs that has been developed based on these advances. These enzymes regulate multiple cellular processes that contribute to tumor development and progression, including cell growth, differentiation, migration, and apoptosis (natural or programmed cell death). Alteration of tyrosine kinase signaling can result in malignant transformation. The human genome encodes 90 proteins with tyrosine kinase domains, and many human tumors, including some breast cancers, display aberrant activation of tyrosine kinases caused by genetic alterations. For tumors whose growth is driven by these activated kinases, targeted drugs can potentially inhibit or reverse malignant progression.

Lapatinib, the latest of the approved tyrosine kinase inhibitors, is a small molecule that was designed to enter cells and selectively inhibit the tyrosine kinase activity of two members of the human epidermal growth factor receptor (HER) family, and is classified as a dual tyrosine kinase inhibitor. Receptor tyrosine kinases are divided into roughly 20 subfamilies, one of which is the HER subfamily consisting of four members: HER1 (ErbB1), HER2 (HER2/neu, ErbB2), HER3 (ErbB3), and HER4 (ErbB4). All members of this family have common structures. The dual inhibitory nature of lapatinib is unique, making the drug a promising addition to targeted cancer therapy. Moreover, metastatic breast cancer eventually develops resistance to trastuzumab and the cancer may return after adjuvant therapy. Early enzyme inhibitors are selective for only HER1 tyrosine kinase, while lapatinib inhibits both HER1 and HER2 including in women with HER2-positive metastatic breast cancer that has progressed after treatment with trastuzumab. HER2 is amplified and overexpressed in 20 to 25 percent of breast cancers. Several studies have demonstrated that breast cancers that overexpress HER2 have a more aggressive course, and higher relapse and mortality rates.

***Survival***. A five-year survival rate for cancer defines the percentage of patients alive at five years after diagnosis, whether disease-free, in remission, or under treatment. It does not imply that five-year survivors have been permanently cured of cancer.

Five-year survival for localized breast cancer (malignant cancer that has not advanced to lymph nodes or other non-breast tissues) has improved from 80 percent in the 1950s to 98 percent today. The five-year survival rate for cancer that has spread regionally (i.e., outside the original site but not to distant sites) is 83 percent. The rate for women with distant metastases is 26 percent. Survival at 10 years for all breast cancer at any stage, combined, is 80 percent, compared to 89 percent at five years.

**Lapatinib (Tykerb)**

Lapatinib has shown promise in results of clinical trials to be an additional tool for treating breast cancer that overexpresses the HER2 protein. Such tumors are particularly aggressive and difficult to treat.

***Mechanism of Action/Activity***. Lapatinib is a potent and reversible inhibitor of tyrosine kinase that mimics ATP and binds to the ATP binding site of tyrosine kinase. As a result, lapatinib blocks ATP from binding to tyrosine kinase and therefore inhibits the enzyme from using ATP as a cofactor for phosphorylation of tyrosine residues. As a result, the drug improves the treatment outcome of advanced breast cancer.

Geyer and associates studied 324 patients with locally advanced or metastatic breast cancer that had progressed after initial chemotherapy plus trastuzumab. Patients were randomly assigned to receive treatment with capecitabine (Xeloda), either alone or in combination with lapatinib. The primary end point was the time to progression, defined as the time from randomization to disease progression or death due to breast cancer. The median time to progression for the capecitabine-only group was 4.4 months versus 8.4 months for the combination-therapy group. The combination-therapy group also showed a higher tumor response rate (22 versus 14 percent), and fewer patients in the combination group had CNS metastases (4 versus 11 patients). There was no difference in survival between the two groups: 22 percent of patients had died by the end of the reported study.

Adverse effects were similar in the two groups except for diarrhea, dyspepsia, and rash, which, as expected, were more common in the combination-therapy group. Adverse events led to discontinuation of therapy in less than 15 percent of patients in either group. Cardiac toxicity was minimal in both groups.

***Adverse Effects***. The safety and adverse effects profile of lapatinib over a wide dosage range has been established in patients with cancer. Overall, lapatinib is remarkably well tolerated. The most frequently reported adverse effects over a dosage range of 500 to 1600 mg daily in Phase I clinical trials were diarrhea (42 percent), rash (31 percent), nausea (13 percent), and fatigue (10 percent). Of 140 reported drug-related adverse events, 135 were mild or moderate and five were judged severe (abdominal cramping, diarrhea, gastroesophageal reflux disease likely due to large pill burdens, rash). In all

**Table 2**
**Patient Information for Tykerb**

- Read the patient information provided by the manufacturer carefully before you start taking this medicine, and each time you get your prescription filled.
- Tell your doctor if you have heart or liver problems.
- Tell your doctor if you have ever had an allergic reaction to Tykerb or any other ingredient of this medicine. A list of ingredients is printed in the patient information leaflet that comes with this medicine.
- Take this medicine exactly as prescribed. The usual dose is 5 tablets taken at the same time once a day, in 21 day cycles. It should be taken at least 1 hour before or after a meal.
- This medicine is to be taken with another medicine called capecitabine (Xeloda), which is taken twice a day.
- The manufacturer warns not to eat or drink grapefruit products while taking this medicine.
- Tell your doctor about all other prescription and nonprescription (OTC) medicines, vitamin/mineral supplements, natural products and herbal remedies you are taking.
- If you forget to take a dose, take it as soon as you remember that day. If you miss a day, do not double your dose the next day. Just skip the missed dose.
- Store this medicine at room temperature in a tightly closed container.
- Women: The manufacturer warns that this medicine may harm an unborn baby. Notify your doctor if you become pregnant or intend to become pregnant. Consult your doctor before nursing a child while taking this medicine.

Phase I studies, the most frequently reported adverse effects at daily dosages up to 1800 mg have been rash, diarrhea, nausea, fatigue, and anorexia. Adverse effects in all published results from Phase II trials are nearly identical to those observed in Phase I trials. The majority of these were either mild to moderate, with one severe adverse event (death secondary to pulmonary embolism) reported as possibly due to lapatinib.

Data from clinical trials indicate that the new drug is safe and generally well tolerated at daily doses up to 1800 mg. Adverse events secondary to lapatinib have been rare in clinical trials.

***Drug Interactions***. Tykerb is likely to increase the action and adverse effects of concomitantly administered drugs that are metabolized by CYP3A4 or CYP2C8. Concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nelfinavir, ritonavir, saquinavir, telithromycin, and voriconazole) should be avoided. If any of these drugs must be given, the physician should consider dose reduction of Tykerb.

Concomitant use of strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital) should be avoided, if possible. If unavoidable, the physician should carefully titrate the dose.

The manufacturer states that patients taking Tykerb should not eat or drink grapefruit products, and should not take St. John's Wort.

***Indications and Uses***. Tykerb is indicated for use in combination with capecitabine for patients with advanced, metastatic breast cancer that is HER2 positive. The combination treatment is indicated for patients who have received prior therapy with other cancer drugs, including an anthracycline, a taxane, and trastuzumab.

***Dosage, Administration, and Availability***. The recommended dose of Tykerb is 1,250 mg orally once daily on Days 1-21 continuously, in combination with Xeloda 2,000 mg/m$^2$/day (administered orally in two doses approximately 12 hours apart) on Days 1-14 in a repeating 21-day cycle. Tykerb should be taken at least one hour before or one hour after a meal. Dividing the daily dose of Tykerb is not recommended. Xeloda should be taken with food or within 30 minutes after food. If Tykerb's dose is missed, the patient should not double the dose the next day. Treatment should be continued until disease progression or unacceptable toxicity occurs. Tykerb is supplied as oval, biconvex, orange, film-coated tablets containing 250 mg of lapatinib.

***Patient Information***. An extensive patient information leaflet is to be dispensed with each prescription for Tykerb; patients are advised to read the leaflet before taking the medication and with each refill. A summary of information to convey to patients is presented in Table 2.

**Overview and Conclusions**

Breast cancer is the most frequently diagnosed cancer in women in the United States and a public health problem worldwide. Tykerb is a dual tyrosine kinase inhibitor with potent activity selective for two members of the human epidermal growth factor receptor family, that are overexpressed in certain breast tumors. The new drug has been well tolerated in numerous clinical trials at therapeutic doses, with the most common adverse events being diarrhea and rash.

# Continuing Education Quiz

This month's questions are taken from the article on "Women's Health: Breast Cancer and its Treatment: Focus on Lapatinib (Tykerb)". Circle your answers to the following questions and mail the entire page to Maryland Pharmacist CE, 650 W. Lombard Street, Baltimore, MD 21201-1572. There is no charge for this quiz for MPhA members (non-members $ 10.00). The completed quiz for this issue must be received by 6/15/10. A continuing education certificate for one and one-half contact hours (0.15 CEUs) will be mailed to you within six to eight weeks. Please type or print clearly. ACPE# 129-144-07-009-H01-P

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The Maryland Pharmacy Continuing Education Coordinating Council is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing education for pharmacists.




1. The earliest sign of breast cancer is most commonly:
   a. breast distortion, scaliness or skin irritation.
   b. abnormalities of the nipple such as retraction.
   c. swelling, tenderness or thickening of breast tissue.
   d. a lump or mass detected on a mammogram.

2. The most common sites of metastases from early breast cancer include all of the following organs EXCEPT:
   a. bone.
   b. liver.
   c. colon.
   d. lungs.

3. The most important factor associated with development of breast cancer is:
   a. age.
   b. family history.
   c. obesity.
   d. progestin therapy.

4. Magnetic resonance imaging (MRI) leads to which of the following when compared to mammography?
   a. Fewer false-positive results
   b. More false-positive results

5. Which of the following is an aromatase inhibitor?
   a. Arimidex
   b. Evista
   c. Herceptin
   d. Tamoxifen

6. Which of the following are used to reduce bone pain and other skeletal events in women with advanced breast cancer?
   a. Aromatase inhibitors
   b. Bisphosphonates
   c. Prostaglandin inhibitors
   d. Narcotics

7. Lapatinib is a potent and reversible inhibitor of:
   a. aromatase.
   b. cytochrome oxidase.
   c. ribonuclease.
   d. tyrosine kinase.

8. The term *apoptosis* refers to which of the following?
   a. Cell differentiation
   b. Cell migration
   c. Cell death
   d. Cell growth

9. Tykerb is indicated for use in combination with:
   a. imatinib (Gleevec).
   b. gefitinib (Iressa).
   c. erlotinib (Tarceva).
   d. capecitabine (Xeloda).

10. The recommended dose of Tykerb is:
   a. 125 mg once daily.
   b. 200 mg every 12 hours.
   c. 1,250 mg once daily.
   d. 2,000 mg every 12 hours.

**Please note: The ACPE Number for "Challenges in Pharmacy Practice: Dispensing Errors and Their Prevention that was in April/May/June 2008 Journal was incorrect. The correct ACPE Number is 129-144-08-001-H05-P.**

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**Farewell Kelly Building**

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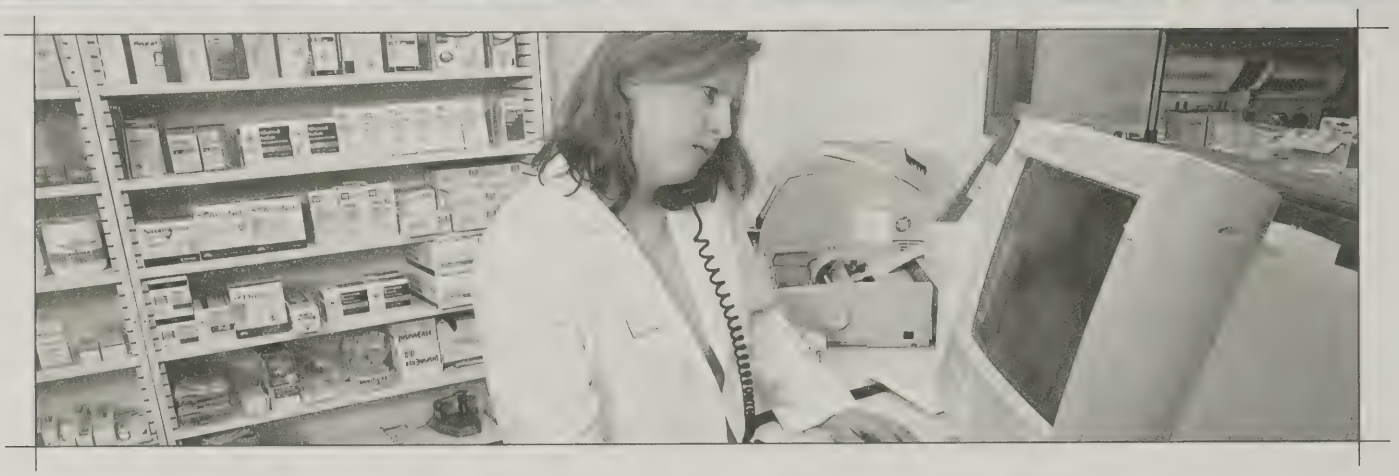
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# Presidents' Message:

## MPhA is on the Move! Farewell to the Kelly Building and Welcome to our New Headquarters.



Magaly Rodreguez de Bittner, Pharm.D.
President

***On February 6, 2009, MPhA held an open house at the Kelly Building for our members. The purpose of this open house was to provide you the opportunity to visit the building and the 1890's and 1950's Museums. It was great to see so many of you come and spend time learning about the history of Maryland pharmacy, our organization and the University of Maryland School of Pharmacy. Many of you bought artifacts that date back many years and tell the story of our profession.***

Many of us had the opportunity to sit for hours at the library and look through books that revealed history of pharmacy many years ago, and that of the pharmacists that contributed to our rich heritage. It was fascinating to look through old yearbooks from the University of Maryland School of Pharmacy and see the faces of many friends and professors that have influenced our lives and our profession. The library symbolized the impact that pharmacy has had in health care and in the discovery of medications. There were formularies dating back to the 1920's. It was interesting to see the medications that we had available back then and the "recipes" for many compounding products.

One of our own, Doug Campbell was able to teach us—and more importantly many of the student pharmacists—the history of so many artifacts that make up the "Baltimore Collection" of the 1890's Museum. We learned that Baltimore had a great impact in the formulation of many products that were used nationwide. We were able to see an old map of Baltimore before the Beltway—Interstate 695—was built. It was clear that pharmacists were important members of the community and had great influence in the advancement of health care in the state.

As sad as it will be to say farewell to our building, it is clear to us that our association is not made of bricks but rather of accomplishments and contributions of its members. It is clear that our strength as a professional association lies in the spirit and dedication of our members. It is evident that the future of our organizations is bright and that we have a great opportunity—as we had in the past—to continue to shape pharmacy practice and health care in the state. Now more than ever, your association needs you. We need you to help us create history in our new headquarters at Montgomery Park. We are retaining some of our historical artifacts to remind us of our rich past, but we also want to fill our new headquarters with new memories and artifacts of our future.

Please join us in making history and shaping the future of our association. There are many ways to get involved, committee memberships, participation in our conventions, volunteer activities and letting us know your opinions and suggestions. We are ready to make history!!

I want to publicly thank our Relocation Committee—Co-Chairs Murlh Flowers and Ginger Apygar, Matt Schimoda, Cynthia Boyle, Butch Henderson, Doug Campbell, Paul Holly, Howard Schiff and Jerry Herpel—for all their hard work with the move and finding our new home.

## Farewell Kelly Building
## Welcome Montgomery Park and Our Future!!

# 2009 Mid-year Meeting in Pictures



# The Pharmacist's Role in Homeopathic Medicine

Eun-Mi Ahn, Pharm.D. Candidate 2009

In ***Profiles of Medical Science and Inspired Moments***, John C. Krantz, former University of Maryland professor with a PhD in Pharmacology, describes his philosophy of self-medication as man's innate need to alleviate pain and take full responsibility of one's own happiness.[1] He goes on to mention that the advancement of health education in laymen increases the wisdom and desire to self-medicate among modern society.[1] Dr. Krantz made these statements over forty years ago and somehow predicted the increased prevalence of OTC and alternative medicine use in today's society.

***An Increasing Trend***

A growing number of the population has turned to holistic approaches to healthcare, thus increasing the exposure and use of homeopathic medicine. These homeopathic remedies can be readily found in most community pharmacies. Therefore, the role of the pharmacist plays an important factor. Many pharmacists are unfamiliar with basic homeopathic information or challenge the validity, safety and efficacy of such drugs.

***Homeopathy 101***

The exact mechanism of action of homeopathic drugs is unknown and is based on the observation that natural substances stimulate the body towards homeostasis. Homeopathic medicines are used primarily to treat symptoms and are not for prophylactic purposes. This is due to the fact that symptoms must first be present to choose the appropriate drug.[3] Nonprescription homeopathic treatment focuses mainly on self-limiting conditions such as headache, cold, flu, fatigue, and nausea.[2]

***Clinical Studies on Homeopathic Medicine***

Clinical trials have been conducted throughout the years to provide evidence based data on the efficacy of homeopathic medicine. The following studies convey positive results of a few homeopathic remedies.

Vickers and Smith examine seven trials that compare the efficacy of homeopathic Oscillococcinum versus placebo in the prevention and treatment of influenza and influenza-like syndromes.[5] There were a total of 2265 participants in the three prevention trials and 1194 participants in the four treatment trials. Only two studies provided sufficient data out of seven studies. The results indicated that there was no evidence to show that Oscillococcinum prevented influenza-like syndrome (RR=0.64 and 95% CI 0.28 to 1.43). However, there was evidence to show that the treatment reduced the length of influenza illness by 0.28 days (95% CI 0.50 to 0.06). The studies show promising results, however they are not strong enough to recommend the remedy for first-line treatment of influenza.[5]

Steinsbekk et al. explore the treatment of upper respiratory tract infection with multiple homeopathic remedies in an open, pragmatic, randomized parallel group, controlled trial.[6] The patients included children under the age of ten who had been to the doctor for URTI. There were 74 participants in the control group and 68 participants in the homeopathic care group. The homeopaths prescribed 22 different remedies, with Calcarea carbonicum being the most prescribed for nearly half of the patients. Some patients were prescribed two, three, or four different medicines at one time. The control group received no placebo or extra consultations over the study period. The 12-week study showed that children receiving individualized homeopathic care had clinically relevant benefits. The median total symptom score showed favorable results for the homeopathic care group (24 points) compared to the control group (44 points) ($p= 0.026$). The number of days with URTI symptoms was statistically significant with 8 days in the treatment group and 13 days in the control group ($P=0.006$).[6] Homeopathic care showed positive and beneficial effects in the prevention of URTI in children.

***The Role of the Pharmacist***

Many pharmacists are skeptical when it comes to the validity of homeopathic remedies and are hesitant to provide counseling for controversial medicines. However, it is the duty of the pharmacist to serve as unbiased health professionals and provide adequate information to the consumer and patient on legally regulated drugs. Since homeopathic drugs fall into this category, pharmacists would benefit from knowing the basics of homeopathy.[4]

Pharmacists should focus on key points regarding homeopathy. The data assessing the efficacy of homeopathy show mixed results.[4] There are a number of reproducible studies that support its efficacy and an equal number of studies that disprove those claims. The extreme dilution of homeopathic substances has rendered most remedies as having little or no active ingredient. Therefore, there is minimal concern for adverse side effects and drug interactions unless the product is contaminated. However, patients may first experience an aggravation of symptoms before seeing signs of improvement. Homeopathic practitioners see this as a positive effect as it indicates the body's natural progression of the healing process.[4]

Pharmacists should be aware that patients and consumers seek their advice and value their opinion. Therefore, it is important that pharmacists evaluate the current literature on homeopathy and decide for themselves if the data is sufficient enough to support its use in practice.

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# Rx AND THE LAW

By Don. R. McGuire Jr., R.Ph., J.D.

**This series, Pharmacy and the Law, is presented by Pharmacists Mutual Insurance Company and your State Pharmacy Association through Pharmacy Marketing Group, Inc., a company dedicated to providing quality products and services to the pharmacy community.**

## COMPARATIVE FAULT

A prior article in this series discussed the elements of negligence which a plaintiff must prove in order to win their case. This article will discuss what occurs when the plaintiff themselves are also at fault in the case.

Under an older theory, this concept was called Contributory Negligence. This is when the plaintiff failed to act as a reasonable person and contributed to their own injury. We could see this occurring in pharmacy cases when the patient clearly recognizes that the tablets in the vial are incorrect, but takes them anyway. The impact that Contributory Negligence has on a case is dramatic. If the plaintiff contributed in any way to their injury, then they are entitled to no damages at all. There are 4 states and the District of Columbia that still use Contributory Negligence in some form. This harsh result may have been modified in those states.

The harshness of the Contributory Negligence concept has led the rest of the states to adopt a Comparative Negligence, or Comparative Fault, system. Under this concept, each party is assigned a percentage of fault with the total being 100%. If our patient above was assessed 10% of the fault in their case, then the verdict would be reduced by 10% and they could only collect 90% of their verdict. This is called Pure Comparative Negligence and is the law in 13 states. Remember the previous result under Contributory Negligence would be that the plaintiff would get nothing in this scenario.

One of the possible results under Pure Comparative Fault is that the plaintiff could be 95% at fault, but still recover 5% of the verdict in their case. This possibility has led some legislatures to modify Comparative Fault. This modification can take several different forms, but essentially bars recovery by the plaintiff if their percentage of fault meets or exceeds a certain threshold. In 11 states, this threshold is 49%, while it is 50% in 21 other states.[1] In these jurisdictions, a plaintiff who is assigned 51% or more of fault will recover nothing. This is reminiscent of the results under Contributory Negligence.

In many ways, Modified Comparative Fault is a balancing act. The potential results under Contributory Negligence can be seen as unfair to the plaintiff who has only a small percentage of fault. On the other hand, allowing plaintiffs to

1 This does not include South Dakota. South Dakota permits recovery by the plaintiff when their fault is slight in comparison to the fault of the defendant, but doesn't assign a percentage to "slight".

proceed with cases where they have a high percentage of fault can be seen as unfair to defendants. Modified Comparative Fault attempts to balance the legal system by not encouraging potentially spurious claims, while at the same time, not discouraging legitimate claims.

In many pharmacy cases, the pharmacy or pharmacist wants to highlight the fact that the patient should have recognized that the tablets in the vial appeared different. This is an attempt to place some fault on the patient. While this argument is theoretically a good one, it does not work well in the real world. First, patients are almost trained to accept, without question, the endless sequence of different generic brands that are dispensed. Secondly, the plaintiff attorney is always quick to point out that if the plaintiff could have recognized the difference, then the trained professional should have been able to recognize the difference also.

Comparative Fault is not always important in pharmacy cases because patients are seldom in a position to seriously contribute to their own injury. However, it can be important in cases where the prescribing physician is a co-defendant. In these cases, fault can be apportioned between the patient, the pharmacy, and/or the prescriber. An example would be a case where the patient is prescribed a drug to which they are allergic. There could be fault apportioned to both the prescriber for prescribing inappropriately and the pharmacy for dispensing inappropriately.

The lesson for the pharmacist here is not that they know if Contributory Negligence or Comparative Fault applies in their state. They need to be aware that this concept exists and that in cases where negligence can be proved, there may be additional factors that will deny the plaintiff recovery or that may allow the pharmacy defendant to pay less than the total verdict. Also, be aware that the claims examiner and/or attorney working on your case will take these factors into account as they work to resolve your case.

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© Don R. McGuire Jr., R.Ph., J.D., is General Counsel at Pharmacists Mutual Insurance Company.

*This article discusses general principles of law and risk management. It is not intended as legal advice. Pharmacists should consult their own attorneys and insurance companies for specific advice. Pharmacists should be familiar with policies and procedures of their employers and insurance companies, and act accordingly.*

# "Therapeutically Speaking..."

## Practice Based Research Networks: A Mechanism to Improve Patient Care

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### What is a PBRN?

The Agency for Healthcare Research and Quality (AHRQ) defines a Practice Based Research Network (PBRN) as "a group of ambulatory practices devoted principally to the primary care of patients, and affiliated in their mission to investigate questions related to community-based practice and to improve the quality of primary care".[1] Currently, there are over 200 PBRNs nationwide and over 100 networks participating in the AHRQ PBRN Initiative, some of which have been in existence for over 20 years.[1,2] In order to be eligible for registration with the AHRQ PBRN registry, the network must have at least 15 practice sites and multiple ongoing projects.[3]

PBRNs are places of learning where groups of clinicians and practices work together with investigators to answer relevant, clinical, community-based health care questions through rigorous research.[4] PBRN research addresses commonly encountered questions that can be studied and answered relatively quickly to produce high quality scientific information that is externally valid and assimilated more easily into everyday practice. Working from multiple practice sites allows a larger sample of patients to be recruited more easily than if one member was recruiting from a single site.[5] PBRN research can also lead to the development of best practice models of clinical services and thus improve patient safety, health outcomes and provider satisfaction.[6] This is possible because PBRNs conduct studies involving representative patients, a broad sample of typical providers, and multiple settings that are characteristic of those expected to adopt these practices.[7] On the other hand, a new drug with demonstrated efficacy in a specific population conducted in a tightly controlled clinical trial setting may not prove to be safe and effective for use in the general population.

### What Entities are Involved in a PBRN?

Many groups of individuals are involved in the development and maintenance of a PBRN. Collaboration is key because no single individual has all the requisite skills or resources to run one alone.[8] Major stakeholders for PBRNs include academic faculty (practice and science), practice site pharmacists, and practice site decision makers. Additionally, PBRNs have network administrators that include but are not limited to a network director, support staff and an advisory committee.[8]

### Do Pharmacy Based PBRNs Currently Exist?

Pharmacy based PBRNs are rare and underutilized. There is a handful of self proclaimed pharmacy PBRNs across the country at this time. Of the more than 100 PBRNs listed on the AHRQ national PBRN registry, only one (The Virginia Community Pharmacy Education and Research Network) indicates that its practice sites are based in pharmacies. The majority of PBRNs are based at primary care or family medicine clinics and involve physicians and nurses.

The Virginia Community Pharmacy Education and Research Network has approximately 27 practice sites (including both independent pharmacies as well as chain pharmacies). Currently, this PBRN is piloting their first project on medication use perception of patients. Jean-Venable "Kelly" R. Goode, PharmD, BCPS, FAPhA, FCCP, the PBRNs network director states that she initiated the pharmacy based PBRN because, "not a lot of research has been published on what pharmacists can do for patients in the community setting." Dr. Goode is "hoping to move community pharmacy practice forward in Virginia by putting a research process behind it and growing a literature base similar to what other medical professions have." She further states that, "this will help improve care for patients in the community."

### What Steps are Involved in PBRN Research?

Once a PBRN is created and enlists all of the major stakeholders listed above, it must implement a continuous quality improvement strategy in order to maintain a certain level of excellence. Four key quality assurance steps are required: plan, do, check, and act. The "planning" step involves identifying areas within a population that need improvement. This information is crucial for developing appropriate research questions for the network. In the "doing" step, the PBRN implements an intervention under controlled circumstances and

collects subsequent resultant data. During the "checking" step, the PBRN monitors and evaluates outcomes of the implemented interventions. In the final "acting" step, the PBRN makes adjustments as needed to improve processes and patient care.[8]

## Where can I get more information about PBRNs?

There are several pharmacy organizations that support practice based research including the American Association of Colleges of Pharmacy (AACP), American College of Clinical Pharmacy (ACCP), American Society of Health System Pharmacists (ASHP) and American Pharmacists Association (APhA).[7] Additional non pharmacy specific organizations have supported PBRNs through recognition and/or funding and include: the National Institutes of Health, AHRQ, the Robert Wood Johnson Foundation, the Institute for Healthcare Improvement, and the Federation of Practice-Based Research Networks.[7] Many of these organizations, including AACP, AHRQ and the Federation of Practice-Based Research Networks have held one or a series of conferences on practice-based research to address the interest in creation of new PBRNs and improvement in function for existing PBRNs. Contact the individual organizations for more information on past or future PBRN programming. Most of the aforementioned organizations also provide a wealth of information on their websites for those looking to learn more.

## How Can I Get Involved with a PBRN?

Networking is the best approach to find others who are interested in practice-based research. Getting involved with local, state and national professional organizations fosters relationships with potential future collaborators.[8]

In order to assess whether it is feasible to initiate a statewide PBRN, a survey was created and distributed to assess interest in and knowledge base of PBRNs among Maryland pharmacists. The survey was sent via email distribution lists to all of the member organizations of the Maryland Pharmacist Coalition (Maryland Pharmaceutical Society, Maryland Pharmacists Association, Maryland Society of Health System Pharmacists, the Maryland Chapter of American Society of Consultant Pharmacists, and the University of Maryland School of Pharmacy Student Government Association). Additionally, the survey was sent to all of the University of Maryland School of Pharmacy preceptors. Ninety-three pharmacists completed the survey. Over 75% of respondents had little or no knowledge about PBRNs, indicating a lack of familiarity and understanding in this area. However, 79.4% of respondents were definitely or probably interested in learning more about PBRNs, 58.7% of respondents were definitely or probably interested in helping to develop a PBRN and 67.1% of respondents would definitely or probably participate in a PBRN, indicating a significant interest. The 3 most common factors influencing one's decision to join a PBRN were time commitment (58.6%), improving outcomes through research (57.5%) and how research fits into daily work flow (57.5%). Potential disease states and practice issues that elicited the greatest response included diabetes (66.3%), hypertension (53.9%), cardiovascular disease (49.4%), patient counseling/education (74.2%), patient safety (70.8%), and patient compliance (69.7%).

*If you are interested in attending a continuing education opportunity on PBRNs, would like to become involved with the creation of a PBRN, or are interested in participating in a Maryland pharmacy PBRN network, please contact Heather B. Congdon at hcongdon@rx.umaryland.edu or 301.738.6344.*

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# Medication Therapy Management: Opportunities and Resources for Pharmacists

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*The MPhA Professional Development Committee ,in an effort to increase awareness and promote opportunities for Medication Therapy Management (MTM) services in Maryland, presents this second article focusing on national and Maryland initiatives and resources for pharmacists to provide MTM services. The first article summarizing the core elements of an MTM service model and perceptions of provider, payer, and patient was published previously in the Maryland Pharmacists Journal, June, July, August 2008, Volume 3.*

MTM services and benefits, unlike written prescriptions or dispensed medications, are intangible products that can only be experienced by the patient or shown through health outcomes data. According to the recent American Pharmacists Association national survey on perspectives of provider, payer and patient, "*data suggest that increasing patient awareness about MTM may increase their appreciation of and desire for these services.*"[1] Naturally, as the most accessible healthcare professional in the community, pharmacists have an excellent opportunity to educate patients about MTM and create demands for these value-added services. Pharmacists should be prepared to provide or at least talk about MTM when patients ask about or request MTM services. This article discusses opportunities, including national and Maryland initiatives and resources for pharmacists to provide MTM services.

## National Initiatives and Resources for Providing MTM

A wealth of national initiatives and resources exist for pharmacists either wishing to implement new MTM programs or build upon their existing MTM practice. Listed below are selected publications and tools available from several pharmacy organizations (APhA, ASCP, NCPA).

### Initiatives and Publications[2,3,4]

- *Core Elements of MTM Service Model.* Version 2.0. A description of MTM with templates for Medication Therapy Review, Personal Medication Record, Medication Action Plan, Intervention and/or Referral, and Documentation and Follow-up.
- *MTM Digest: Perspectives on MTM Service Implementation.* An evaluation of the strategies associated with MTM implementation and the value of MTM services to provider, payer and patient.
- *MTM Promotional Flyers.* Handouts for patients, payers, and other providers to explain MTM services and benefits.
- *Electronic versions of articles* originally printed in *Pharmacy Today* on a variety of MTM topics.
    - Measuring success in your MTM practice
    - Primer: Billing for services - Medicare and beyond
    - Implementing MTM: Getting your game plan together
    - Creating demand for patient services
- *APhA Foundation Diabetes Ten City Challenge.* An innovative program for partnership between employers and communities, in which pharmacists are compensated for diabetes management to reduce overall health care costs.

### Resources and Training Tools[3,5,6]

- *MTM Self-Assessment Tool.* In 10 minutes, assess readiness to provide MTM services.
- *MTM Certificate Training Program.* A comprehensive certificate training plus 21 hours CE program designed to help pharmacists implement and practice MTM.
- *MTM Monograph Series.* A CE program on different disease-states for pharmacists providing MTM.
- *Medication Management Tool Kit for Assisted Living.* A tool for pharmacists who provide or wish to provide MTM services in assisted living communities.
- *MTM in the Independent Community Pharmacy.* A specific program for pharmacists in independent pharmacies.

## Maryland Initiatives and Strategies for Expanding MTM

In a collaborative effort to expand MTM services in Maryland, the MD-ASCP, MPhA, and University of Maryland School of Pharmacy implemented a *Pharmacists and Preceptors MTM Training Initiative* with the following goals: (1) optimize medication use and improve public health, (2) provide certificate training for pharmacists, preceptors and student pharmacists, and (3) advance pharmacy practice in community and long-term care settings.[7]

This initiative offers the APhA-ASCP MTM certificate training program and forms a network for pharmacists and preceptors who provide and/or teach MTM services throughout Maryland. Since its creation in September 2007, there have been four training sessions at different locations (University of Maryland School of Pharmacy at both the Baltimore and Shady Grove Campuses; Rocky Gap Resorts in Western Maryland; and pending in Eastern Shore Maryland) for over 90 pharmacists and preceptors in a variety of practice settings. In addition, 30 student pharmacists in the final professional year requested for the MTM certificate training program to be offered as an elective course at University of Maryland School of Pharmacy. If you are interested in becoming certified in MTM, please contact Hoai-An Truong at htruong@rx.umaryland.edu.

The *Maryland P3 Program* (Patients, Pharmacists, Partnership), is a collaboration with employers and payers in which pharmacists receive compensation for cognitive services. Pharmacists work in collaboration with the enrolled patients' healthcare team to control and improve the patient's chronic diseases while reducing overall health care costs. The program began operation in Cumberland in 2006 and was a part of the *APhA Foundation Diabetes Ten City Challenge*. It has since expanded to five additional employer sites and is one of several nationally recognized programs that utilize pharmacists to help patients with individual care focusing on education and self-management training.[8] If you are interested in becoming involved with the P3 program, please contact Christine Lee at clee@rx.umaryland.edu.


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# ADHD and Its Treatment in Adults

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**Goal.** The goal of this lesson is to explain attention-deficit/hyperactivity disorder (ADHD) in adults with focus on its clinical characteristics and confirmation, and its treatment.

**Objectives.** At the conclusion of this lesson, successful participants should be able to:

1. recognize epidemiologic information and characteristics relevant to ADHD;
2. identify symptomatology that characterizes ADHD and the principles that govern its clinical confirmation and management in adults; and
3. select from a list specific nonpharmacologic and pharmacologic measures that are reported to modify signs and symptoms of ADHD in adults.

Attention-deficit/hyperactivity disorder (ADHD), which affects up to 12 percent of children and adolescents, persists into adulthood in up to 60 percent of cases. Four to 5 percent of adults worldwide are affected, making ADHD one of the most common psychiatric conditions in adulthood for which treatment is available.

Only recently has the persistence of untreated ADHD in adults been recognized in primary care. Marked by inattention, distractibility and impulsivity, clinical features of adult ADHD are reminiscent of the symptoms of childhood ADHD; however, the condition



Gossel



Wuest

evolves and changes as the individual matures.

Work productivity loss in adults with ADHD is estimated at 35 days each year. Annual health care costs for adults with ADHD, compared with an age-matched cohort of unaffected adults, are three times higher, and annual health care expenditures for their family members are approximately 1.9 times higher compared with a matched cohort (group consisting of shared characteristics) of family members of non-ADHD patients.

## Background

In adults, ADHD can lead to substantial social and occupational impairment and is associated with increased familial stress. Fewer adults with ADHD are employed full time, indicating that those with ADHD have a lower average income than control subjects, regardless of academic achievement or personal characteristics.

Adults with ADHD have been shown to be more careless drivers, and more likely to receive multiple citations for speeding and have their driver's license revoked. Adults with ADHD are twice as likely to have been arrested and convicted of a crime.

Only 47 percent of adults with ADHD report being satisfied with their family life, compared with 68 percent of those without the condition. Adults with ADHD are twice as likely to be divorced. Only half of affected adults report contentment with their professional life.

Adolescents with and without ADHD have the same rate of substance abuse; such is not the case for adults with ADHD. Between adolescence and adulthood, the rate of substance abuse increases substantially for individuals with ADHD.

Although parents may worry that treating ADHD with psychostimulants will predispose their children to substance abuse later in life, treatment may actually protect against the development of substance abuse. If ADHD is consistently and effectively treated during the childhood and adolescent years, the risk of substance abuse later in life is no greater than in the general population.

ADHD may affect sexual behavior. The Milwaukee Young Adult Outcome Study showed that sexually transmitted disease was four times more prevalent among persons with ADHD than their non-affected peers. Affected persons also had far more children by age 20, but only half of the ADHD

**Table 1**
**Top ten symptoms of adults with ADHD that lead to self-referral to a physician**

1. Poor concentration
2. General disorganization
3. Tendency to leave projects incomplete
4. Inattention
5. Poor school performance
6. Problems with time management
7. Difficulty controlling temper
8. Impulsive
9. Anxiety
10. Difficulty functioning at work

*Adapted in part from Faraone SV, Spencer TJ, Montano B, Biederman J. Arch Intern Med. 2004;164:1221-1226.*

parents retained custody of their children.

Executive functioning (the ability to maintain appropriate problem solving activity for attainment of a future goal) is an area of intense research in the study of ADHD. Problems present clinically as deficits in time management, organization, and sequential and hierarchical thinking. Exceptionally intelligent adults are often able to compensate for their inabilities through adolescence and even young adulthood, but the cumulative challenges may eventually overwhelm their compensatory mechanisms.

Data describing the likelihood that a child with ADHD will also have the disorder as an adult are conflicting. As definitions of ADHD subtypes improve, some subtypes will likely be found that cause more adult dysfunction than others.

## Pathogenesis

As in childhood and adolescent ADHD, the most critical neurotransmitters in adults with ADHD are the catecholamines dopamine and norepinephrine, both of which appear to regulate inhibitory influences in the frontal-cortical processing of information. Specific neurobehavioral roles for these neurotransmitters remain unclear. Both dopamine and norepinephrine act upon relatively specific pathways that regulate attention, concentration and other cognitive functions. It is theorized that dopamine enhances signals and improves attention, acquisition, focus, on-task behavior and cognition, perception and vigilance. Norepinephrine may diminish "noise;" decrease distractibility and shifting; improve executive operations; and increase behavioral, cognitive, and motor inhibition. In terms of pathophysiology, it is postulated that neurotransmitter dysfunction causes dysregulation of the inhibitory influences of frontal-cortical activity, which is predominantly regulated by norepinephrine, and of lower striatal structures, which are predominantly dopaminergic. These striatal structures are driven by dopaminergic agonists controlled or modulated by higher inhibitory structures sensitive to adrenergic agents.

## Clinical Confirmation in Adults

There are no efficient standardized assessment tools to specifically identify adult ADHD, which makes diagnosis confirmation challenging. Extensively studied in children, its persistence into adulthood was not recognized until the mid-1970s. These symptomatic adults were diagnosed retrospectively with ADHD following interviews with their parents and determination that symptoms of illness characteristic of the disorder had indeed been noticed during the affected adults' early years.

Current guidelines for both children and adults are that patients must meet the criteria established by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). Symptoms are categorized as follows: inattention (difficulty sustaining attention), forgetfulness and distractibility; hyperactivity (fidgeting, excessive talking and restlessness) and impulsivity (difficulty waiting one's turn and frequent interruption of others). The DSM-IV criteria also include onset by age seven (confirmed, possibly, by retrospective analysis), impaired functioning in at least two settings (home, work, school), and persistence beyond six months.

**Symptoms.** Symptoms in adults are similar to those in childhood except they are usually less disruptive and more along the lines of a sense of inner restlessness. Typically, adults with ADHD are unaware that they have the disorder. They may feel it is difficult to get organized, to stick with a job or keep an appointment. Everyday tasks of arising in the morning, getting dressed and ready for the day's work, arriving at work on time and being productive on the job can be major challenges for the ADHD adult. Problems may intensify in adulthood when they begin an independent life with increasing challenges for organization associated with marriage, parenting, occupational planning and administration.

Adults almost always self-refer for treatment rather than having a physician suggest its presence initially. This may occur when their children are diagnosed with the disorder and they begin to understand that some of the traits that have troubled them for years might point to ADHD as the root cause of their problems. Other adults seek professional help for anxiety or other symptom(s) listed in Table 1. They may have a history of social inadequacy or problems at work, or they have been involved in frequent automobile accidents and they seek answers for the root cause of their "problem." Gender distribution of self-referring adults is nearly equal.

A presenting comorbidity (concomitant, but unrelated illness) may be the first clue to the presence of adult ADHD. The majority of adults with ADHD have at least one additional psychiatric disorder such as anxiety, bipolar disorder or major depressive disorder; some adults may have more than one. Because there is considerable

symptom overlap, this creates the potential for diagnostic confusion with consequent tendency to disguise a diagnosis of ADHD. It is also possible that many adult patients with ADHD have clinically significant but subthreshold symptoms.

Hyperactivity symptoms may decrease with age because of developmental trends toward self-control. Adults with ADHD are generally less hyperactive than children. Whereas young children can often be seen in purposeless climbing, jumping and running about, adult variants of these characteristics include such traits as being a workaholic, feeling uncomfortable sitting through meetings or a movie, being unwilling to wait in line, and speeding while driving. Affected adults often work overtime and/or hold more than one job. Symptoms of hyperactivity in adults may also be based not so much on motor behavior but on other aspects of functioning, such as talking. Adults may feel they need to talk excessively or they regularly talk out of turn, blurt out inappropriate comments, or feel compelled to talk endlessly on their cell phone during meetings or while driving. Such behaviors can lead to both personal and professional harm. Inattentive symptoms do not appear to have a similar developmental advantage and they tend to remain constant throughout adulthood.

Adults with ADHD may be unable to understand which of their actions provoke irritation in others, but advancing age does have an advantage in that they may have better insight into monitoring the reactions of others and so they adjust their behavior accordingly. Traits that were problematic in childhood may be adaptive to selective jobs by an adult. This does not imply that these adults no longer suffer impairment in quality of life, social relationships, personal planning, underemployment, motor vehicle safety and other dimensions of functioning. As one adult wisely said, "You don't grow out of ADHD; you just get better at coping with it!" It stands to reason that adults with ADHD experience life differently from persons without ADHD.

## Treatment

Pharmacotherapy of adult ADHD is an effective means to manage symptoms of the disorder, with approximately two-thirds of adult patients experiencing moderate-to-marked improvement with drugs when combined with psychoeducational management. Clinical trials have confirmed that medications positively improve core ADHD symptoms by enhancing levels of dopamine and/or norepinephrine.

**Stimulants.** The two major stimulant categories used to treat ADHD are the amphetamines and methylphenidates, compounds with a similar clinical effect. Stimulants comprise the majority of treatment protocols for both children and adolescents, and for adults. Seventy-five to 80 percent of adults with ADHD responded positively to stimulants in short-term trials. It is reported that 1.5 million adults in the United States now take stimulants on a daily basis to treat their ADHD, with 10 percent of users older than 50 years of age.

Amphetamines include dextroamphetamine (d-amphetamine; Dexedrine, etc.) and mixed amphetamine salts (Adderall, etc.). Recent advances have occurred with delivery systems rather than new and novel drugs. Long-acting formulations allow for more convenient and confidential administration of medication and eliminate the possibility of forgetting to take midday doses. They also reduce peak and trough adverse effects such as headache and moodiness, and eliminate afternoon wear-off and rebound. An extended-release form of mixed amphetamine salts (Adderall XR) provides 10 to 12 hours of activity. Lisdexamfetamine (Vyvanse ), approved in 2007 for use in children, may become another alternative therapy for adults. Lisdexamfetamine is composed of d-amphetamine combined with the amino acid lysine that renders the molecule inert. Gastric enzymes cleave the lysine, which activates the molecule. Since gastric enzyme exposure is necessary for activation, this ensures that the medication cannot be misused if snorted or injected intravenously. Lisdexamfetamine is also long-acting and has consistent pharmacodynamic properties.

Methylphenidate is available in immediate-release (four-hour duration of action), longer acting (six- to eight-hour duration), and extended-release (10- to 12-hour duration) formulations. Osmotic-release oral system (OROS) methylphenidate (Concerta ) releases the active ingredient slowly over 12 hours. Dexmethylphenidate (Focalin ) is comprised solely of the dextro- (active) portion of the methylphenidate molecule. Products are available in immediate- and extended-release formulations. The methylphenidate transdermal system (Daytrana) is an alternative to orally-administered drugs that delivers the active ingredient via skin patch. With optimal wear time of nine hours each day, its duration of action persists up to three hours after the patch is removed.

Adverse effects of stimulants are generally mild and can be managed by adjusting the medication timing and dosage. The most common short-term effects are diminished appetite, GI disturbance, headache, insomnia and motor disturbance.

**Non-stimulants.** Atomoxetine (Strattera) is a highly selective norepinephrine reuptake inhibitor in presynaptic neurons; it reduces reuptake of dopamine in prefrontal lobes to a lesser extent. It is of interest that development of atomoxetine was initially piloted in adults rather than children, although confirmation of benefit in children followed. At present, it is the only non-stimulant with FDA approval for treatment in adults. It often takes longer than the stimulants to achieve clinical effect, but has a powerful anxiolytic effect and minimal abuse potential. Atomoxetine is generally well tolerated with few mild side effects including appetite

**Table 2**
**Helpful websites for adult ADHD***

| | |
|---|---|
| www.cdc.gov | Centers for Disease Control and Prevention |
| www.chadd.org | Children and Adults with Attention-Deficit/Hyperactivity Disorder |
| www.nami.org | National Alliance on Mental Illness |
| www.nimh.nih.gov | National Institute of Mental Health |

*Enter *Adult ADHD* and *search*.

suppression and insomnia.

Antidepressants are considered a second choice for treatment of adults with ADHD following a trial with the stimulants and atomoxetine. The older antidepressants (tricyclics) are sometimes used because they modify norepinephrine and/or dopamine. Venlafaxine (Effexor), a non-tricyclic antidepressant, is also used for its enhancement effect on norepinephrine. Bupropion (Wellbutrin, etc.), an antidepressant with an indirect effect to increase central dopamine, has been useful in treatment of ADHD in both children and adults. It has the added benefit of aiding reduction of nicotine dependence.

**Education and Psychotherapy.** Although pharmacotherapy provides needed support, the individual must succeed on his own. To assist in this struggle, both education and individual psychotherapy can be helpful. Adults can learn how to organize their life by posting a large calendar where it will be seen each morning that lists important tasks for the day. A special place can be set aside for keys, bills and the paperwork of everyday life. Tasks can be organized into segments such that completion of each part can give a sense of accomplishment. Above all, adults with ADHD should learn as much as they can about their disorder so they understand what is going on in their body and, thus, be better equipped to manage it.

Psychotherapy can be a useful adjunct to medication and education, Therapy can help patients improve their poor self-image by examining experiences that produced it. The therapist can encourage patients to adjust to changes in their life by treatment – the loss of impulsivity and desire for risk-taking, and the new feeling of thinking before acting. As patients begin to understand their new ability to organize the complexities of life, they can often begin to appreciate characteristics of ADHD that are positive, such as new-found energy, warmth, and enthusiasm.

Focused therapies that incorporate cognitive-behavioral features have reportedly been effective in children, adolescents and adults with ADHD. The benefit of these treatments without concurrent pharmacotherapy has yet to be determined.

**Drug Holidays.** Drug holidays, common in treatment of childhood ADHD, may also become part of the pharmacotherapy of adult ADHD. However, there is growing consensus that this practice of withholding medication one or more days each week in adults is inappropriate and that medication is most effective when taken consistently without interruption.

**Adherence.** Poor adherence with treatment is common in the care of adult patients initiating stimulant therapy. In one study, adults initiating pharmacological treatment for ADHD continued their medications for an average of only 50 days. Although early discontinuation of treatment commonly occurs in the care of adult ADHD, the factors that promote continuity of stimulant treatment remain largely unknown.

Optimal management of ADHD includes pharmacologic and nonpharmacologic interventions. Support groups help persons of all ages with ADHD and their family members understand the disorder and available resources. Support groups can be located by calling an ADHD hotline (800.233.4050) or by contacting Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD) (Table 2). Other helpful websites on ADHD are also listed in Table 2.

## Summary and Conclusions

Adult ADHD is one of the most common psychiatric disorders. It differs from ADHD in children and adolescents in that adults can often modify their daily routines to better match their temperament. It has been shown in most clinical trials that pharmacologic treatments effective in children and adolescents are also effective in adults. Although adults with ADHD are at higher risk for substance abuse than adults without the disorder, recent studies have shown that pharmacotherapy may reduce the risk of substance abuse in adults with ADHD.

• • • • • • • • • • • • • • • • •

The content of this lesson was developed by the Ohio Pharmacists Foundation, UPN: 129-000-08-009-H01-P. Participants should not seek credit for duplicate content.

# Continuing Education Quiz

This month's questions are taken from the article on "ADHD and Its Treatment in Adults". Circle your answers to the following questions and mail the entire page to Maryland Pharmacist CE, 650 W. Lombard Street, Baltimore, MD 21201-1572. There is no charge for this quiz for MPhA members (non-members $ 10.00). The completed quiz for this issue must be received by 9/15/11. A continuing education certificate for one and one-half contact hours (0.15 CEUs) will be mailed to you within six to eight weeks. Please type or print clearly.
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1. Work production loss in adults with ADHD is estimated at:
   a. 15 days each year.
   b. 35 days each year.
   c. 55 days each year.
   d. 75 days each year.

2. Between adolescence and adulthood, the rate of substance abuse for individuals with ADHD:
   a. increases.
   b. decreases.

3. The most critical neurotransmitters in adults with ADHD are dopamine and:
   a. acetylcholine.
   b. gamma-aminobutyric acid.
   c. norepinephrine.
   d. serotonin.

4. Which of the following in NOT listed as a function regulated by dopamine and/or the neurotransmitter referred to in question # 3?
   a. Concentration
   b. Attention
   c. Perception
   d. Memory

5. Which of the following statements is true?
   a. Adults almost always self-refer for treatment of ADHD.
   b. Physicians almost always suggest the presence of ADHD in adults initially.

6. Which of the following statements is most likely to be true about adults with ADHD?
   a. They understand which of their actions provoke irritation in others.
   b. They are not able to adjust their behavior to the reaction of others.
   c. They do not suffer impairment to quality of life or social relationships.
   d. Traits that were problematic in childhood may be adaptive to selective jobs.

7. The percentage of adults with ADHD who responded positively to stimulants in short-term trials has been:
   a. 55 to 60 percent.
   b. 65 to 70 percent.
   c. 75 to 80 percent.
   d. 85 to 90 percent.

8. Which of the following products is comprised solely of the dextro- (active) portion of the methylphenidate molecule?
   a. Strattera
   b. Focalin
   c. Dexedrine
   d. Concerta

9. Which of the following products is a non-stimulant drug?
   a. Strattera
   b. Focalin
   c. Dexedrine
   d. Concerta

10. There is growing consensus that the practice of withholding ADHD medication one or more days each week in adults is:
   a. appropriate.
   b. inappropriate.

**Please note: The ACPE Number for "Challenges in Pharmacy Practice: Dispensing Errors and Their Prevention that was in April/May/June 2008 Journal was incorrect. The correct ACPE Number is 129-144-08-001-H05-P.**

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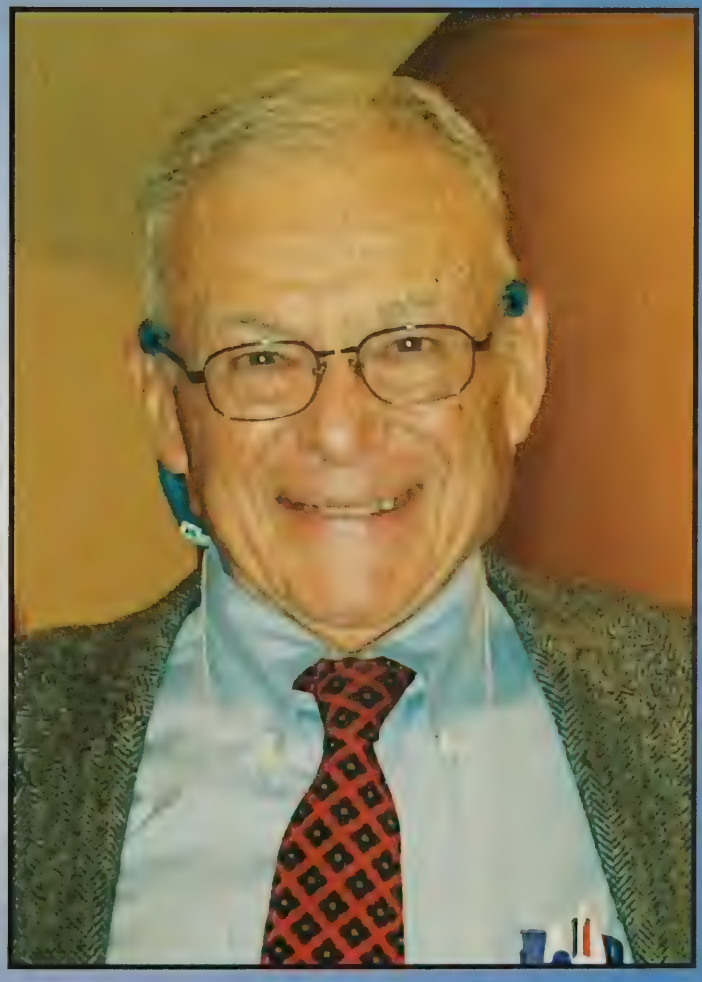
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## In Memorial

After a brief illness Joe, our attorney, friend, and advocate for more than 55 years passed away on August 1. Joe represented pharmacists in legal affairs, both large and small, always with a smile on his face and always aggressively. He would take the cases others avoided gravitating to the underdog and defending them against perceived abuses by government agencies and large corporations. Frequently, he refused to accept payment for services and only asked that his clients be members of MPhA. He handled the affairs of the Association and spoke at our meetings–the last time in June. There were few like him; he will be sorely missed.



**Joseph S. Kaufman, Esq.**

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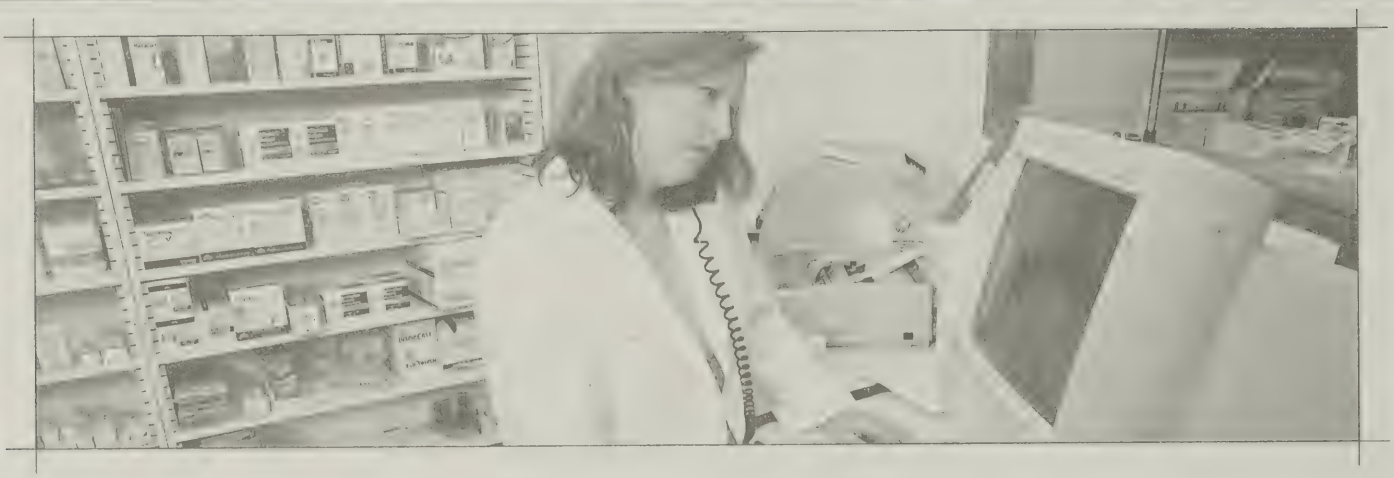
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# Presidents' Message



Magaly Rodreguez de Bittner, Pharm.D.
President

Dear MPhA members:

It has been my pleasure to serve as your President for the past year. It has been a very exciting year and a significant one for our organization. As I reflect back on the major accomplishments or issues that we addressed last year, I wanted to highlight some of them:

1. Kelly Building: With the decision to sell the lease at the Kelly Building, I appointed a Relocation Committee back in June 2008. This past year we were able to finalize the sale to UMMS. While this was an emotional journey, we are excited about the potential that these funds provide MPhA to continue to fulfill our mission. The Relocation Committee led the work to secure space for MPhA and the Museum at another location. We successfully secured rented space at Montgomery Park and the 1890 Museum was loaned on a permanent basis to the University of Maryland School of Pharmacy and it will be displayed in the new Pharmacy Hall Addition. Many other museum pieces and artifacts were given on permanent loan to the Schools of Pharmacy at Notre Dame and UMES.
2. Outreach to other organizations: We were able to reach out to other professional organizations such as Med Chi and MSHP. We present at a meeting with MedChi concerning the role of the pharmacists in the Maryland P3 Program and Immunizations. In addition, we created a joint committee between MSHP and MPhA for joint professional programming and pharmacists training. This committee is planning activities to promote collaborative practice and other training programs in Diabetes and MTM.
3. Visibility of MPhA: I was able to attend a round table discussion for Health Care Reform. Our message related to the role of the pharmacists as medication experts and the need for adequate reimbursement for pharmacy services, including dispensing.
4. Appointment of new committees: Two new Committees were formed, the Strategic Planning Committee and the Bylaws Review Committee. The existing Membership committee established a facebook and on-line membership registration, the Communication Committee created a new format for the "Monday Message", the Professional Committee conducted a variety of training programs and the Convention Committee attracted excellent speakers for our meeting.

As I finalize this article, I wanted to THANK all the committee chairs and members for their hard work and dedication to our organization. Let's remember this is a voluntary activity. Additionally, I need to THANK each one of you, our members, for allowing me the opportunity to serve as your President. I look forward to my new role as Chairman of The Board of Trustees.

As I stated throughout the year, ***MPhA is on the Move, lets seize the opportunity***! Our Association has made great strides this past year, even when we had to dedicate a lot of time to issues concerning our relocation. We gained new members, we have formed important committees to revise our Bylaws and Strategic Plan, and we have an energized new Board with many new practitioners who are excited to serve you and our Profession. We want to invite you to become active in YOUR Association and join us in building pharmacy's future, especially, with the upcoming Health Care Reform.

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# Therapeutically Speaking...

## Warfarin Therapy: Part 1

## To Fill or Not to Fill: Warfarin Review and Therapy Assessment in a Community Patient

**Katie Kiser, Pharm.D., BCPS**
**Assistant Professor, University of Maryland School of Pharmacy**

***Mr. Z is a 76 year old African American man with a history of atrial fibrillation and hypertension. He has been a patient of yours for a long time and comes in today for a refill on his warfarin, HCTZ, and enalapril. He also brings in a new prescription for amiodarone. Mr. Z states, "I just saw my cardiologist and he took me off the metoprolol and replaced it with this new medication for my heart. I'm not sure if it's ok to take with my other medications or not." Mr. Z also states, "And I heard on the news last night that spinach is a super-food and is really good for you; however I was told when I started the warfarin to stay away from the green leafy vegetables. Do you think it's alright if I start eating spinach twice a week?"***

1. ***What concerns, if any, do you have about Mr. Z's medications and his question about starting to eat spinach twice a week?***
2. ***What questions would you ask Mr. Z and what actions would you take?***

***This case will be used throughout the article to review warfarin pharmacology, management, drug interactions, and patient education.***

**Indications**[1]
Warfarin is an anticoagulant commonly used to prevent and treat blood clots. In Mr. Z's case, he is on warfarin for stroke prevention secondary to atrial fibrillation. Other conditions that require treatment with warfarin to prevent and/or treat blood clots include mechanical heart valves, venous thromboembolism, pulmonary embolism, myocardial infarction, and inherited or acquired clotting disorders.

**Mechanism of Action**[1]
Warfarin is pharmacologically classified as a vitamin K antagonist. It inhibits an enzyme called Vitamin K Oxide Reductase (VKOR) in the production of vitamin K-dependent clotting factors, II, VII, IX, and X. Warfarin also inhibits our body's natural anticoagulants, protein C and protein S. This mechanism of action leads to a prolongation in the time it takes for the blood to form a clot. This time is measured as prothrombin time (PT), which is then mathematically converted into the international normalized ratio (INR) to standardize the results between labs and different institutions.

**Basic Pharmacokinetics of Warfarin**[1]
First to cover some basics pharmacokinetic information about warfarin: it has high bioavailability with rapid absorption and a low volume of distribution (due to being highly protein bound to albumin). It is made up of a mixture of both R and S enantiomers, with the S enantiomer being 3 to 4 times more pharmacologically active than the R. Warfarin is hepatically metabolized; the S enantiomer through CYP 2C9 and the R enantiomer through CYP 1A2 and 3A4. It is then eliminated mainly through urine and bile as inactive metabolites.

**Genetic Factors**[1]
There is currently much research surrounding genetic factors that affect warfarin metabolism (including CYP 2C9 polymorphisms) and warfarin sensitivity (including VKOR abnormalities). In general, Caucasians and Asians are more likely than African Americans to have either decreased warfarin metabolism or increased sensitivity and thus require lower doses. It has not yet been established if or when genetic testing should be used in routine warfarin management.

**Clinically Important Drug and Food Interactions**[1,2]
Drug interactions may be classified as either pharmacokinetic (what the body does to the drug), which includes absorption, distribution, metabolism, and elimination (ADME), or pharmacodynamic (what the drug does to the body). Due to the numerous drug-drug interactions with warfarin, it is impossible to review all clinically important ones in this

article; please refer to a reference like Micromedex® or Facts and Comparisons® for comprehensive drug interaction information.[3,4]

**Table 3** demonstrates how several different agents change pharmacokinetic parameters of warfarin and thus influence the INR.

| Agent | | Change in ADME | Expected Change in INR |
|---|---|---|---|
| Bile Acid Sequestrants | | ↓ Absorption of warfarin | ↓ |
| Phenytoin, Metronidazole | | ↑ Distribution of warfarin | ↑ |
| 2C9: Rifampin<br>Phenobarbital<br>Carbamazepine<br>Phenytoin | 3A4: St. John's Wort<br>Rifampin<br>Phenytoin<br>Phenobarbital<br>1A2: Tobacco smoke | ↑ Metabolism of warfarin | ↓ |
| 2C9: Amiodarone<br>Fluvastatin<br>Trimethoprim/ Sulfamathoxazole<br>Fluconazole<br>Metronidazole | 3A4: Clarithromycin<br>Fluconazole<br>Gemfibrozil<br>Fluoxetine<br>Cimetidine<br>Ritonavir | ↓ Metabolism of warfarin | ↑ |

**Table 3: Warfarin Drug Interactions Based on Pharmacokinetic Parameters**

Some pharmacodynamic drug interactions include herbal products like gingko, ginger, and garlic (the 3 G's). These have been shown to increase the INR secondary to a decrease in platelet aggregation.[2] Pharmacodynamic drug interactions that can decrease the INR include vitamin K and ginseng. Vitamin K, as described above, is essential in the production of clotting factors II, VII, IX, and X. If vitamin K intake increases, then there are more vitamin K-dependent clotting factors for warfarin to compete against and the INR will decrease and vice versa. Most drug interactions can be managed by close INR monitoring and/or empiric warfarin dosage adjustment.

**Monitoring of Therapeutic and Toxic Effect**

The normal range for the INR is 0.8 - 1.2. During anticoagulation the therapeutic INR range varies, but is typically between 2 - 3 for patients with atrial fibrillation or venous thromboembolism and between 2.5 - 3.5 for patients with mechanical heart valves. For Mr. Z, since he has atrial fibrillation, his goal INR range is 2 - 3.

**Table 1** shows the different subjective and objective information that can be used to monitor and assess the therapeutic and toxic effects of warfarin in atrial fibrillation.

| | Subjective Data | Objective Data |
|---|---|---|
| **Therapeutic Effect** | Signs or Symptoms of Stroke<br>▪ One-sided numbness or weakness<br>▪ One-sided facial droop<br>▪ Loss of vision<br>▪ Difficulty speaking<br>▪ Difficulty walking | INR 2 – 3 |

| | | |
|---|---|---|
| **Toxic Effect** | Signs or Symptoms of Bleeding<br>▪ Nose bleeds<br>▪ Blood in sputum<br>▪ Blood in stool or urine<br>▪ Dark, tarry stools<br>▪ Large, dark bruises without cause | INR > 3<br>Hemoglobin drop > 2 g/dL<br>Hematocrit drop > 4%<br>Hemoccult test (blood in stool) |

**Table 1: Warfarin Therapy Monitoring Grid for Atrial Fibrillation**

**Warfarin Dose Adjustment**[5]

Multiple factors may contribute to an INR that is less than or greater than the therapeutic goal range. Some of these factors include missed or extra doses of warfarin, new prescription or over-the-counter medications or changes in doses, changes in alcohol or vitamin K intake, and illness. If the patient specific subjective and objective data lead the provider to decide the warfarin dosing needs to be adjusted, then there are several different approaches. A provider could hold or change the dose for one to several days and then resume the previous regimen or change the regimen. If a provider decides to change the regimen, the general approach taken is to increase (if the INR is low) or decrease (if the INR is high) the weekly dose of warfarin by 5 to 20%. The percent change is based on the distance of the INR from therapeutic range, patient specific data including sensitivity to dose changes in the past, age, concomitant medications, etc., and the clinical experience of the provider.

**Table 2** summarizes guideline recommendations on how to approach elevated INRs.

| INR | Bleeding Present | Rapid INR Reduction Needed | Management |
|---|---|---|---|
| < 5 | No | No | Omit dose; decrease dose regimen when INR is therapeutic |
| 5 – 9 | No | No | Omit one or two doses; decrease dose regimen when INR is therapeutic |
| | | Yes (high risk) | Hold dose and give 1 – 2.5mg oral vitamin K; may repeat; decrease dose regimen with INR is therapeutic |
| | | Yes (surgery) | Hold dose and give 2.5 - 5mg oral vitamin K to reduce INR in 24 hours; may repeat with 1 – 2mg oral; decrease dose regimen when resume |
| > 9 | No | No | Hold dose and give 5 - 10mg oral vitamin K to reduce INR in 24 to 48 hours; may repeat; decrease dose regimen when INR is therapeutic |
| Any | Yes (Serious) | Yes | Hold dose and give 10mg vitamin K by slow IV infusion; may repeat every 12 hours; supplement with fresh frozen plasma, prothrombin complex, or recombinant factor VIIa |

**Table 2: Management of Supratherapeutic INRs**

**Adapted from** Ansell, J, Hirsh, J, Hylek, E, et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:160-198.

**Patient Case Wrap-up**

Recall Mr. Z was taking warfarin, HCTZ, enalapril, and now amiodarone. From **Table 3** we can see that amiodarone is an inhibitor of CYP 2C9 and thus decreases the metabolism of S-warfarin and can significantly increase the INR. Historically, the dose of warfarin would be empirically decreased by about 50% to account for this drug interaction. Before dispensing, verification with the provider of the drug interaction and plan for close warfarin management and

monitoring is a necessary action to take. Also, patient counseling and general education about warfarin, amiodarone, and the drug interaction is very important.

Remember Mr. Z also would like to start eating spinach two times a week, but was told to avoid vitamin K containing foods. This old myth is just that, a myth! Patients should be encouraged to be informed about what foods have high vitamin K content (see **Table 4** for some examples) and to be consistent about how many times per week they eat them. It is fine for Mr. Z to eat vitamin K containing foods as long as he discusses this change with his provider first, and then continues to eat spinach or another high vitamin K content food consistently two times a week. If he ever decides he would like to eat more or less servings per week, he would need to discuss this again with his provider.

As Mr. Z's pharmacist, you have a critical role to play in his safe and effective use of warfarin therapy. Do not underestimate the impact that you can make with assessment of appropriate anticoagulation monitoring and follow-up, medication therapy review for drug interactions, and patient counseling and education.

**Table 4: High Vitamin K Foods**

| Food | Serving Size |
|---|---|
| Broccoli | 1/2 cup |
| Brussels Sprouts | 5 sprouts |
| Cabbage | 2/3 cup fresh boiled |
| Cole Slaw | 3/4 cup |
| Collard Greens | 1/2 cup boiled |
| Kale, cooked | 1/2 cup |
| Leaf Lettuce, raw | 2 cups |
| Spinach | 1/2 cup boiled |

***Edited by:***
***Mary Lynn McPherson, Pharm.D., BCPS***
***Professor, University of Maryland School of Pharmacy***

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[1] Jacobs L. Warfarin Pharmacology, Clinical Management, and Evaluation of Hemorrhagic Risk for the Elderly. Cardiol Clin 2008;26:157-167.

[2] Coumadin [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2007.

[3] Micromedex Healthcare Series. Thompson Micromedex. Copyright 1974-2008. http://www.thomsonhc.com.proxy-hs.researchport.umd.edu/hcs/librarian

[4] Facts and Comparisons 4.0. Wolters Kluwer Health, Inc. Copyright 2008. http://online.factsandcomparisons.com.proxy-hs.researchport.umd.edu/index.aspx?

[5] Ansell, J, Hirsh, J, Hylek, E, et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:160-198.



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# *Therapeutically Speaking...*

## Warfarin Therapy: Part 2

### Managing Warfarin Therapy Throughout the Continuum of Care

**Allison Chilipko, PharmD Candidate, Class of 2009, Nicole Brandt, PharmD, CGP, BCPP, FASCP, Associate Professor, University of Maryland School of Pharmacy**

In the preceding article, Mr. Z, a 76 year old man, is taking warfarin and concerns exist regarding a drug interaction between amiodarone and his warfarin. Older adults use over the counter (46%) and herbal supplements (52%) of the time while taking prescription medications and 50% of them are noted to have a drug interaction with anticoagulants. This leads to approximately 1 out of 25 older adults at risk for significant drug-drug interaction.[1] This is the case with Mr. Z who experienced a thromboembolic event due to a sub therapeutic INR because of his concomitant use of St. John's Wort and increased spinach intake.

Warfarin management in older adults is challenging not only because of polypharmacy [2] but also because of age related changes. Warfarin pharmacokinetics may be altered through changes in hepatic function, protein binding, and volume of distribution placing an older adult at greater risk for adverse effects. This is further complicated by impaired vision, dexterity and cognition which may interfere with their ability to manage medications such as warfarin. .

Generalized estimates for hemorrhagic risk associated with warfarin therapy in clinical practice range from 1.5% to 6.5%.[4] In the context of this substantiated bleeding propensity, investigations with targeted older adult study populations have demonstrated even higher magnitudes of risk given the aforementioned demographics.[3,4,5] A retrospective investigation by Johnson et al. analyzed the adverse consequence incidence in seniors aged 75 years or older who were maintained on warfarin therapy for chronic atrial fibrillation and had experienced at least one hospitalization in the preceding year (not necessarily from anticoagulation-related complications) as an indication of the vulnerability of this population subset. After 530 years of collective follow-up, enrolled patients experienced 53 major hemorrhages, for an annual 10% rate, 13 life-threatening bleeding episodes, and 5 fatal hemorrhages.[5] In comparison, the atrial fibrillation investigators revealed an annual 1.3 % rate of major hemorrhage in a younger population with a subset of patients 75 years of age or older. [5]

Benefits of anticoagulation in older adults may never be achieved due to practitioner reluctance to titrate starting doses to the appropriate maintenance range for therapeutic INR achievement. [4, 5] Despite a 94% consensus among surveyed physicians that older adults should receive anticoagulation for chronic atrial fibrillation, only 40% of patients were receiving therapy.[3]

From the community to other areas of care, pharmacists are in a pivotal position to identify all factors that could cause an interaction as well as maximize efficacy of warfarin while minimizing adverse consequences. This article will discuss initiatives and opportunities for pharmacists throughout various practice settings as well as continue the case of Mr. Z.

**Hospital-Oriented Models**

Now that Mr. Z has entered the hospital due to a thromboembolic event, let's review the opportunities for pharmacists as well as initiatives that influence practice. Pharmacist interaction with patients receiving anticoagulation may traverse the inpatient or outpatient divisions, especially in consideration of care transfers. From the inpatient aspect, pharmacists may be responsible for providing recommendations on anticoagulation therapy as a member of the interdisciplinary care team. Data from a pharmacist-led multidisciplinary team investigation, in which pharmacists performed risk assessments to consider anticoagulation candidates for stroke prophylaxis with atrial fibrillation, portrayed the value of pharmacy incorporation within the care team for appropriate medication utilization.[7] During the hospital stay, 60 patients necessitated "upgrades" from no therapy to anticoagulant addition or dosage optimization, whereas 18 cases resulted in a dosage reduction due to toxicity concerns.[7] At discharge, fewer patients remained on anticoagulation in reference to critical pharmacist analysis and decision-making among potential treatment alternatives.[7]

With regard to outpatient care, pharmacists may demonstrate figurative ownership or participate within anticoagulation clinics.[3,4] Studies have shown that pharmacist run anticoagulation clinics reduces venous thromboembolic events, decreases bleeding-related complications, enhances therapeutic INR targeting on repeated monitoring evaluations, and decreases overall health care costs from emergency department and hospital admissions.[4,5]

These clinical successes coupled with the Joint Commission standards have created a niche for antithrombotic therapy within the overreaching medication safety guidelines in the recently released 2009 National Patient Safety Goals

(NPSGs).[8] Under the generalized third goal to "improve the safety of medications", NPSG 03.01 provides the foundation for regulatory concern regarding the prevalence and severity of adverse consequences and drug interactions.[8] NPSG 08.01.01 addresses medication reconciliation across the continuum of care to safeguard against medication misadventures that often surround high risk medications such as warfarin..[8] In correlation with the patient safety goals, further pipeline developments feature a performance measure initiative to optimize anticoagulation management with the "National Consensus Standards for Prevention and Care of Venous Thromboembolism".[9]

Fortunately, Mr. Z's thromboembolic event has been treated but due to his immobility while in the hospital, he has decompensated. He is being transferred to a nursing home for additional physical therapy with the goal of eventually being back in his own home.

**Long-Term Care Applications**

Despite the plethora of opportunities for anticoagulation development within hospital pharmacy, the long-term care environment has been rather slow to adopt pharmacist-led anticoagulation services. In the nursing home, all residents do receive a monthly medication regimen review from a pharmacist but very few LTC facilities have pharmacist driven anticoagulation services seen in the hospital or ambulatory setting. Pharmacists should be cognizant of warfarin dosing changes, reports of bleeding from nursing and physician notes, and routine laboratory results in order to assess and provide therapeutic recommendations to optimize care during at least their monthly review. Mr. Z's nursing home and consultant pharmacist have an established monitoring plan to try to minimize adverse consequences and avoid medication errors. Mr. Z has remained therapeutic and will be discharged home to the community where he will once again navigate the healthcare system independently.

**Community Pharmacy Opportunities**

Mr. Z has completed the continuum of care and now truly knows the importance of optimal control of his warfarin management and may look to his community providers for additional support. Currently, all pharmacist-driven anticoagulation clinics are hospital-based without extension to the community setting.[10] A major barrier to enlarging existing MTM chronic disease state management programs through anticoagulation incorporation stems from the absence of laboratory monitoring due to stringent Maryland limitations regarding point-of-care testing. However, pharmacists can attempt to dissipate this obstacle through an extensive mutual relationship with surrounding physician practices to enhance the flow of information and communication as well as evolving technological advances with electronic medical records and increased accessibility among health care divisions.[11] Under the scope of MTM, pharmacists could be reimbursed through select Medicare Part D plans for 1) annually reviewing warfarin prescriptions for compliance and adverse consequences, 2) intervening when necessary and contacting the provider with dosage changes, and 3) participating in comprehensive medication reviews to analyze drug utilization and counsel on dietary factors and potential drug-drug interactions.[12,13]

As a complement to traditional physician services, supportive evidence has already illustrated the pharmacist's capability to beneficially modulate outcomes in outpatient clinic settings. An investigation by CG et al. followed patients for 6 months after transitioning from pharmacist-managed clinics to physician-based office care.[4] Researchers observed a significant decrease in number of INRs within the target range (76% vs. 48%), increase in health care utilization (2 emergency department visits before transition vs. 13 medical care referrals with 6 emergency department visits after transition), and enhanced patient satisfaction with pharmacist-directed care.[4] In confirmation of these results, CL et al. portrayed a reduction in warfarin's adverse consequences with pharmacist management by following patients for 6 months after anticoagulation clinic discontinuation.[3] During the study period, enrolled patients revealed an increased number of adverse events (3 vs. 14), patients experiencing adverse events (3 vs. 10), and, total hospitalized days.[3]

**Current and Emerging Roles for Pharmacists:**

In evaluating this risk assessment, pharmacists, regardless of realm of specialization, have the potential to contribute to anticoagulation management in their own distinct care pathways through the underlying commonality of providing direct patient care to older adults. Pharmacists from different backgrounds can become Certified Anticoagulation Care Providers through examination passage with the National Certification Board for Anticoagulation Providers.[13] Furthermore, web-based applications may foster discussion beyond pharmacy channels to the various health care entities through the Anticoagulation Forum.[14] In the absence of operating an anticoagulation clinic, pharmacists will consistently be exposed to and responsible for monitoring and counseling on warfarin.

The MTM model has revolutionized the delivery of pharmaceutical care by allowing pharmacists to utilize their clinical knowledge and training as a marketable and reimbursable cognitive severe to enhance health-related outcomes and decrease inappropriate utilization of health care resources.[13] Despite firm establishment of anticoagulation

management through hospital affiliation, adaptation of this outpatient clinic schematic to long-term care and community pharmacy has not been fully embraced given perceived and actual barriers and the absence of justifiable statistics to warrant further progression.[14] Refer to Table 1 for potential sequential steps for implementing an MTM service within your own practice venue.[11,12,13]

**Conclusion**

Despite warfarin's efficacy as an oral anticoagulant, this agent continues to exude prominence within medication error reports, inappropriate health care utilization, and adverse consequences. In summation, this article offers an overview for pharmacist operation in accordance with novel standards and regulations to enhance the delivery of anticoagulation. Although pilot studies have been conducted regarding community-based anticoagulation management, to date, this foundation has not been reconciled in the absence of definitive models, pharmacoeconomic analyses, and direct evidenced-based outcomes of pharmacist intervention.[13,14] Individuals like the case of Mr. Z are increasing in number and pharmacists need to play an increasingly active role to minimize healthcare expenditures and preserve older adult's quality of life.

**Table 1: Algorithm for Anticoagulation MTM Implementation[11, 12,13,14]**

| Pharmacy Practice Site: | Procedural Elements for MTM Realization: |
|---|---|
| Nursing Homes and Assisted Living Facilities | ✓ Assess the number of residents receiving anticoagulation<br>✓ Evaluate existing monitoring systems for warfarin therapy<br>✓ Discuss potential implementation and feasibility with the medical team<br>✓ Work with your pharmacy provider to develop a monitoring form and protocol (consider indication, target INR range, duration of therapy, and flow sheet for tracking INR results)<br>✓ Review the established form with the medical director and director of nursing to elicit feedback<br>✓ Work to implement the final revision as the standardized monitoring form for medication administration record placement<br>✓ Develop an in-service presentation to educate nursing staff on form completion and review anticoagulation monitoring<br>✓ Rewrite anticoagulation monitoring protocols for form inclusion<br>✓ Track form utilization and evaluate the domains of the form for continuous quality assurance<br>✓ Utilize the form during resident chart review to ensure regulatory compliance |
| Community-Based Disease State Management | ✓ Take an inventory of the number of patients at the practice site receiving anticoagulation, type of Medicare Part D insurance, and primary care providers<br>✓ Survey patient interest regarding anticoagulation management services, current satisfaction with anticoagulation care, and flexibility to change<br>✓ Work with corporate advisors and clinical program coordinators to develop a sustainable clinical and business model<br>✓ Contact local providers to begin relationship development, referral service, and transmission of laboratory results<br>✓ Secure protocol compliance with regulatory agencies and governances<br>✓ Apply for the monetary support to obtain vital resources<br>✓ Consider practical elements for time allowance, support staff designation, and actual facility<br>✓ Gain MTM certification and obtain a national provider identifier<br>✓ Contract with an independent reimbursement platform or utilize the Centers for Medicare and Medicaid Services 1500 billing form<br>✓ Engage in annual reviews of warfarin therapy for identified patients<br>✓ Schedule and conduct comprehensive medication reviews<br>✓ Communicate recommendations with predetermined providers<br>✓ Document clinical services and outcomes for research purposes<br>✓ Consistently evaluate the process to allow for improvement<br>✓ With a sustainable model, expand to reach more patients and providers |

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# Hemorrhagic Stroke: Prevention and Treatment

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**Goal.** The goal of this lesson is to discuss hemorrhagic stroke with focus on its clinical characteristics and treatment.

**Objectives.** At the conclusion of this lesson, successful participants should be able to:

1. recognize epidemiologic information and clinical characteristics relevant to hemorrhagic stroke;
2. identify symptomatology that characterizes hemorrhagic stroke and the principles that govern clinical confirmation and management; and
3. select from a list specific therapeutic measures that are reported to modify signs and symptoms of hemorrhagic stroke.

## Background

Every year in the United States, 700,000 persons suffer from stroke, and 200,000 of these events are recurrent. Approximately 270,000 persons die each year in the United States because of stroke, ranking it third in mortality behind heart disease and cancer. Hemorrhagic stroke (intracranial hemorrhage) accounts for approximately 13 percent of all strokes. Hemorrhagic stroke not only has a high case fatality, but also limited treatment options and a poor, most often disabling, outcome. Stroke leads to more long-term disability than any other disease process, and burdens the U.S. healthcare system by a reported $57.9 billion each year.



Gossel



Wuest

## Subarachnoid Hemorrhage

**Epidemiology.** Subarachnoid hemorrhage (SAH) accounts for 21,000 to 22,000 strokes each year in the United States, affecting young adults predominantly. The risk for women is 1.6 times that of men, and the risk for African-Americans is 2.1 times that of whites. The average mortality rate is 51 percent. Approximately one-third of survivors require lifelong care. Most deaths occur within two weeks after the event, with 10 percent occurring before the patient reaches a medical facility and 25 percent within 24 hours after the stroke. Overall, SAH accounts for 5 percent of deaths from stroke, but for 27 percent of all stroke-related years of potential life lost before age 65. One-half to two-thirds of survivors report a decrease in their quality of life.

A number of risk factors for SAH have been identified. Hypertension, a well established risk factor for ischemic stroke, is less well characterized as a risk factor in SAH.

**Pathogenesis.** Nontraumatic SAH is a neurologic emergency characterized by bleeding into spaces surrounding the brain that are normally filled with cerebrospinal fluid (CSF). Recall that the brain and spinal cord are covered by three layers of connective tissue, termed the meninges, and encased in bone. The outer layer of the meninges is the *dura mater*, the middle layer the *arachnoid*, and the inner layer the *pia mater*. The arachnoid is a thin, delicate membrane. Separating the arachnoid from the pia mater is the subarachnoid space that contains CSF, which serves to cushion the brain and spinal cord. Bleeding into the subarachnoid space initiates a series of events that lead to spasms of the cerebral blood vessels. Spasm can significantly constrict these vessels, resulting in diminished cerebral blood flow. Blood flow is inversely proportional to the fourth power of the radius, so small changes in the vessel size can produce deleterious effects. If blood flow is reduced below the critical level needed to maintain membrane integrity, cerebral ischemia with edema formation and infarction may follow. Regional cerebral edema further compromises local blood flow causing further ischemia despite an overall normal intracranial pressure.

The principal causes of SAH are rupture of aneurysms and arteriovenous malformations (AV anomalies). Trauma can also cause subarachnoid bleeding. Ruptured aneurysms are the cause in 85 percent of patients.

**Saccular Aneurysms.** Saccular ("berry") aneurysms are thin-

walled outpouchings that protrude from arteries. They gradually enlarge and can ultimately rupture. Multiple aneurysms are found in about 15 percent of affected persons. Since the incidence of aneurysmal SAH is approximately one in 10,000, it is clear that most saccular aneurysms do not rupture. Surgical morbidity far exceeds these percentages. Following rupture, rebleeding is an early and devastating complication. Intracranial aneurysms, unless giant (greater than 1.5 cm in diameter), are usually asymptomatic. An estimated 5 to 15 percent of cases of stroke are related to ruptured intracranial aneurysms.

**Clinical Characteristics and Confirmation.** SAH should be suspected in persons complaining of a sudden onset of severe headache along with nausea and vomiting, neck pain or stiffness, photophobia and loss of consciousness. The classic symptom is a rapidly developing, severe headache. Patients typically describe it as the "worst headache of my life" or "like a hammer blow." In three out of four patients, onset occurs within a few seconds. It is the only symptom in about a third of patients. Headache from SAH is usually diffuse. Prodromal (warning) headaches may precede the actual SAH by several weeks in over 40 percent of cases. It is however, not the severity, but the suddenness of onset, which is the characteristic feature of SAH, a feature that patients may fail to mention because it is the severity of pain for which they seek medical attention. SAH is believed to be misdiagnosed in up to half of persons being evaluated for the first time. The most common incorrect diagnoses are migraine and tension-type headache.

Arterial pressure is often elevated and body temperature increased, especially during the first few days after bleeding since subarachnoid blood products produce chemical meningitis. Nearly half of all victims experience transient changes in mental status.

A number of neurologic complications can occur if a patient does not die immediately after a SAH. Some result from blood in the subarachnoid space. Other complications include rebleeding from the same aneurysm, cerebral vasospasm and its resulting ischemia leading to reduced blood supply, hydrocephalus (excessive accumulation of fluid in the cerebral area) from blockage of CSF outflow, and seizures. Non-neurologic complications include cardiac and electrolyte abnormalities.

Survivors of SAH may experience chronically disabling problems. More than half report problems with memory, mood or neuropsychological function. These deficits result in impairment of social roles, even in an absence of apparent physical disability. Up to two-thirds of survivors return to work by one year after a SAH.

**Treatment.** Patients with SAH should be evaluated and treated on an emergency basis. Following stabilization, they should ideally be transferred to a center with a dedicated neurologic critical care unit to optimize care. The primary goals of treatment are prevention of rebleeding, prevention and management of vasospasm, and treatment of accompanying medical and neurologic complications.

Medical management of a ruptured aneurysm is intended to reduce the risk of rebleeding and cerebral vasospasm and to prevent other medical complications before and after surgical intervention. The patient is provided general support including bed rest, gentle sedation as needed, analgesics for headache and stool softeners to minimize straining. Glucocorticoids may help reduce the headache and neck stiffness and/or pain caused by blood in the subarachnoid space. There is no solid evidence that they reduce cerebral edema, are neuroprotective or reduce vascular injury in SAH; their routine use is therefore not recommended. Hypertension, if present, should be treated but not aggressively since elevated blood pressure may be a normal compensatory mechanism, especially in a chronically hypertensive patient. At present, there is no conclusive evidence whether modifying blood pressure in acute SAH benefits the patient.

The calcium channel antagonist nimodipine (Nimotop) has an established role in decreasing vasospasm in all grades of SAH. A review concluded that calcium channel antagonists decrease the proportion of patients with poor outcome and ischemic neurological deficits after aneurysmal SAH. The results relating to poor outcome depend on one large trial, but against the background of the potentially devastating consequences of vasospasm, the use of nimodipine is indicated in all patients with non-traumatic SAH and should be started as soon as the diagnosis is made. A dose of 60 mg should be given every four hours orally or via a nasogastric tube. Nimotop carries a boxed warning to not administer the drug intravenously or by other parenteral routes because deaths and serious life threatening adverse events have occurred when the contents of the capsules have been injected parenterally. Blood pressure should be kept in the "high-normal" range in attempt to maintain cerebral perfusion pressure. If hypotension occurs, the dosage regimen may be changed to 30 mg every two hours.

## Primary Intracerebral Hemorrhage

Nontraumatic intracerebral hemorrhage (ICH; within the brain substance) occurs mainly as a result of chronic, poorly controlled hypertension; spontaneous ICH refers to those cases that occur in the absence of trauma. A ruptured vascular malformation is responsible less often. Despite evidence that ICH is more than twice as deadly as SAH, clinical and laboratory research continues to focus primarily on SAH. Unlike the declining mortality with SAH due to improvements in surgical and critical care techniques, morbidity and mortality with ICH have remained

relatively unchanged over the past several decades.

**Epidemiology.** Primary ICH is one of the most devastating forms of stroke, and is responsible for about 80 percent of all intracranial hemorrhages in the United States, affecting approximately 67,000 Americans each year. ICH has the distinction of having the highest mortality rate of all types of stroke. Morbidity and mortality associated with ICH are dismal, with 30-day mortality ranging between 30 and 40 percent in hospital-based studies to as high as 52 percent in community-based studies. The annual mortality rate following 30-day survival was 8 percent per year for five years in one community-based study with almost half of all later deaths attributed to complications of the original hemorrhage. Only 21 to 28 percent of patients with ICH could live independently after six months.

The risk for primary ICH is estimated to be about twice as high in African-American, Hispanic and Japanese populations than in Caucasians. The reason for the large discrepancy among populations is unclear. Alcohol consumption and low serum cholesterol levels have been theorized to account for some differences in the Japanese population. There is a slight predominance of men with ICH versus women.

**Pathogenesis.** ICH is bleeding that occurs directly into the brain parenchyma (the functional tissue, as opposed to connective tissue). It is differentiated from intraventricular hemorrhage and SAH, which involve bleeding into the brain's ventricular system and subarachnoid space, respectively. ICH is classified as primary (unrelated to congenital or acquired lesions), secondary (directly related to congenital or acquired conditions), and/or spontaneous (not secondary to trauma or surgery). ICH typically consists of a large area of hemorrhaged blood that clots. Most hemorrhages occur at or near bifurcations of arteries (the point at which a vessel divides into two branches). The blood is slowly removed over the next several weeks by phagocytosis, and after several months, only a small collapsed cavity may remain. Large hemorrhages typically rupture into the ventricles with bleeding into the subarachnoid space.

It is believed that the initial hemorrhage encircles intact neural tissue, which causes neurologic deterioration attributed to the development of cerebral edema. This appears within hours secondary to the clot releasing plasma proteins into the underlying white matter. Later, delayed thrombin formation may contribute to neural toxicity directly or through damage to the blood-brain-barrier indirectly with subsequent worsening of edema. Peak edema occurs three to seven days following the hemorrhage along with lysis of erythrocytes. Both hemoglobin and its degradation products have been implicated in neural toxicity. The importance of cerebral edema in ICH has been supported by evidence suggesting that patients with a larger amount of cerebral edema relative to the initial hemorrhage volume have a very poor prognosis. Evidence from serial contrast computed tomography (CT) scans show that hematomas can continue to expand over many hours and is the natural course of disease progression. Bleeding may cease when the lesion gets to a size sufficient to produce increased tissue compression (tamponade).

Hypertension is the most important risk factor for ICH especially in persons younger than 55 years of age. It is estimated that approximately 25 percent of ICH events would be prevented if all hypertensive patients received adequate antihypertensive therapy to maintain normal pressure. Smoking, excessive chronic alcohol consumption (more than two drinks/day), and cocaine use (especially in persons older than 45 years) also increases the risk. It is unknown why cholesterol levels less than 160 mg/dL increase the risk.

Warfarin anticoagulation remains a highly effective therapy for prevention of thromboembolic stroke in persons with atrial fibrillation. Anticoagulation to an International Normalized Ratio (INR) of 2.5 to 4.5 has been associated with risk of ICH of approximately 1 percent per year for stroke-prone patients. On the other hand, this rate is nearly 10 times greater than the risk of hemorrhage in a matched group of persons who have not undergone anticoagulation. When such hemorrhages occur, the fatality rate averages 60 percent. Predictors are advanced age, prior ischemic stroke, hypertension, and intensity of anticoagulation therapy.

ICH is the most feared complication of thrombolytic therapy used in acute myocardial infarction or stroke. When a recombinant tissue plasminogen activator (rt-PA) (e.g., alteplase/Activase) is administered within three hours after onset of ischemic stroke symptoms, the ICH rate is 6.5 percent, compared with 0.5 percent in placebo patients. Half of the individuals who sustain these hemorrhages die. The overall benefit of rt-PA therapy in appropriate patients with ischemic stroke is more than counterbalanced by the risk of hemorrhage.

**Clinical Manifestations and Confirmation.** Although not associated with exertion, ICH usually occurs when the patient is awake and sometimes when stressed. The classic presentation is sudden onset of a focal neurologic deficit that progresses over minutes to hours with accompanying headache, nausea and vomiting, elevated blood pressure and decreased consciousness. The neurologic abnormalities are similar to those caused by ischemic stroke since destruction of neural tissue is the root cause of the dysfunction that results from either entity. Specific signs and symptoms are determined by the location of the lesion. Since the site of ICH often differs from ischemic stroke, characteristic patterns of neurologic loss may be more frequently associated with ICH

**Table 1**
**Clinical features of intracerebral hemorrhage**

| | Site of Hemorrhage | | | |
|---|---|---|---|---|
| **Symptom** | **Putamen** | **Thalamus** | **Pons** | **Cerebellum** |
| Unconsciousness | Later | Later | Early | Late |
| Sensory change | Yes | Yes | Yes | Late |
| Pupils | | | | |
| Size | Normal | Small | Small | Normal |
| Reaction | Yes | Yes or No | Yes or No | Yes |
| Response to nutrition | Yes | Yes | No | Yes or No |
| Ocular bobbing | No | No | Sometimes | Sometimes |
| Gait lost | No | No | Yes | Yes |
| Vomiting | Occasional | Occasional | Often | Severe |

Adapted from Zivin JA. *Textbook of Medicine*, 22 ed. Philadelphia:Saunders;2004:2298-2305.

than with ischemic stroke. Hemorrhages may continue to enlarge over several hours as bleeding continues. Ischemic lesions, on the other hand, usually do not change in size following vascular occlusion. As a result, hemorrhages characteristically cause increasing loss of neurologic function with time until a plateau is reached, whereas ischemic strokes may remain static or fluctuate after the early phases of the stroke. About one-fourth of patients who initially are alert may show subsequent deterioration in their level of consciousness after an ICH. ICH in each of the four typical locations within the brain produces characteristic findings (Table 1).

ICH often cannot be confirmed based on clinical findings alone. The test of choice for assessing the type of stroke is CT. Head CT provides substantial information including the size and location of the hemorrhage, and the presence of intraventricular, subarachnoid or subdural blood. It differentiates ICH from nonhemorrhagic cerebral infarctions and may reveal underlying structural abnormality. Magnetic resonance imaging (MRI) is sensitive for ICH; it is useful for dating hemorrhages and identifying small vascular lesions that may be missed with conventional CT. MRI is limited in early detection of ICH, time required to obtain imaging and by the limited ability to monitor patients while in the scanner.

**Treatment.** No surgical or medical treatment has proved effective, although an estimated 7,000 surgeries to remove hemorrhaged blood are performed in the United States each year. Supportive treatment is the usual means to manage acute ICH, with early care given to maintenance of airway, oxygenation and nutrition, and treatment of secondary complications. Clinical trials of corticosteroids, glycerol and hemodilution (increasing plasma volume in relation to erythrocytes), have not demonstrated benefit. Corticosteroids, in fact, may increase the risk of infectious complications. There is no accepted means for management of increased intracranial pressure. Hyperventilation, neuromuscular paralysis and osmotherapy (treatment by the intravenous injection of hypertonic solutions to produce dehydration) are without significant benefit. Fluid management should maintain a normal volume (euvolemia). Seizures should be treated despite a lack of data from randomized trials, since they can be particularly harmful for critically ill patients. Maintenance of normal body temperature is desirable and fever should be aggressively treated with acetaminophen or cooling blankets since fever may accelerate tissue destruction.

**Prognosis.** Most early deaths result from the direct neurologic consequences of the hemorrhage. The severity of bleeding (e.g., size, extension into ventricles) and level of neurologic function are the best predictors of poor outcomes. Long-term prognosis for various degrees of recovery is similar or better than that of cerebral infarctions of comparable severity. The risk of recurrent ICH has not been well studied, but the risk of at least one rebleed may be as high as 25 percent over the next several years. The risk of ICH can be reduced by appropriate treatment although there is no specific therapy. Control of mild to moderate hypertension decreases the risk of hemorrhagic stroke by one-third to one-half.

## Summary and Conclusions

All patients with suspected stroke require rapid assessment and intervention. Assessment aims to establish the diagnosis of stroke and its etiological subtypes, and to estimate the prognosis for complications, recurrent events, survival and handicap. Intervention strives to reverse any ongoing brain hemorrhage or ischemia, lessen the risk of complications and recurrent stroke, and optimize physiological homeostasis and rehabilitation.

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# Continuing Education Quiz

This month's questions are taken from the article on "Hemorrhagic Stroke: Prevention and Treatment". Circle your answers to the following questions and mail the entire page to Maryland Pharmacist CE, 1800 Washington Blvd., Suite 333, Baltimore, MD 21230-1701. There is no charge for this quiz for MPhA members (non-members $10.00). The completed quiz for this issue must be received by 12/15/11. A continuing education certificate for one and one-half contact hours (0.15 CEUs) will be mailed to you within six to eight weeks. Please type or print clearly.
ACPE# 129-144-08-012-H01

Name_____

Address_____

City, State, Zip_____

Daytime Phone_____

Date Completed _____
(*Required*)

The Maryland Pharmacy Continuing Education Coordinating Council is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing education for pharmacists.

1. Most deaths from subarachnoid hemorrhage (SAH) occur within:
   a. two minutes.
   b. two hours.
   c. two days.
   d. two weeks.

2. The arachnoid is the thin, delecate membrane that constitutes which of the following layers of the meninges?
   a. Inner
   b. Middle
   c. Outer

3. The principal causes of SAH are arteriovenous malformations and rupture of:
   a. aneurysms.
   b. plaque.
   c. arterioles.
   d. granulomas.

4. The classic sympton of SAH is severe:
   a. cramping
   b. depression
   c. headache.
   d. syncope.

5. General support for patients experiencing an SAH include all of the following EXCEPT:
   a. antiemetics.
   b. analgesics.
   c. sedatives.
   d. stool softeners.

6. Spontaneous intracerebral hemorrhage (ICH) refers to those cases that occur in the absence of:
   a. syncope.
   b. symptoms.
   c. thromboembolism.
   d. trauma.

7. The bleeding associated with ICH occurs directly into the brain parenchyma which is:
   a. connective tissue.
   b. functional tissue.
   c. interstitial tissue.
   d. mesenteric tissue.

8. The most important risk factor for ICH, especially in persons younger than 55 years of age, is:
   a. hyperkalemia.
   b. hyperlipidemia.
   c. hypertension.
   d. hyperthrombosis.

9. The root cause of the dysfunction that results from either ICH or isschemic stroke is:
   a. destruction of neural tissue.
   b. initiation of arterial fibrillation.
   c. precipitation of ventricular tachycardia.
   d. rupture of atherosclerotic plaque.

10. Which of the following has been proven to be effective in treating ICH?
   a. Medical treatment only
   b. Surgical treatment only
   c. Both medical and surgical treatment
   d. Neither medical nor surgical treatment

# 2008 Recipients of the "Bowl of Hygeia" Award




Wyeth Pharmaceuticals takes great pride in continuing the "Bowl of Hygeia" Award Program developed by the A. H. Robins Company to recognize pharmacists across the nation for outstanding service to their communities. Selected through their respective professional pharmacy associations, each of these dedicated individuals has made uniquely personal contributions to a strong, healthy community which richly deserves both congratulations and our thanks for their high example.

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MARYLAND
# Pharmacist
VOLUME 85 NO. 3

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**Therapeutically Speaking . . .**
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**Continuing Education**
*Schemic Stroke: Prevention and Treatment*



**Frank (Butch) Henderson, P.D.**
**President**
**2009 - 2010**

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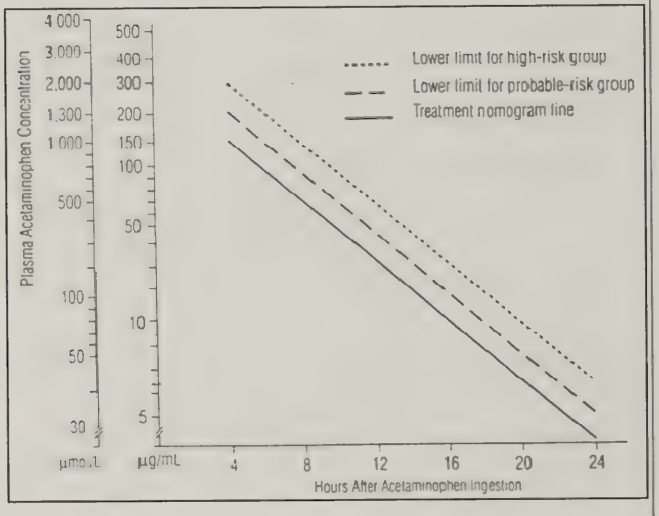
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toxtidbits
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October 2009

# Acetaminophen: A New Approach to an Old Problem

The approach to acute acetaminophen poisoning is changing.

Over the last four years, several cases of acute acetaminophen overdoses have had delayed peak plasma concentrations (>4 hours post-ingestion) and/or double peaks. This had rarely been described before. Meanwhile, the antidotal management of these overdoses has at times been shortened, especially when intravenous acetylcysteine is administered. As a result of delayed peaks and shorter treatment, more cases of hepatotoxicity following acute acetaminophen overdoses are being reported. More frequent monitoring of plasma acetaminophen concentrations is necessary.




The Maryland Poison Center will recommend obtaining a minimum of two plasma acetaminophen concentrations 4-hours apart for all acute intentional overdoses involving ANY acetaminophen product. We recommend monitoring the plasma concentrations until the peak and downward trend have been documented. In many respects, the monitoring of plasma acetaminophen will closely parallel that of aspirin, valproic acid, carbamazepine and most other readily measurable substances.

Any plasma acetaminophen concentration plotting above the "Treatment line" on the Rumack-Matthew nomogram is considered potentially hepatotoxic. These patients should receive antidotal therapy. Plasma acetaminophen concentrations obtained *before* 4 hours post ingestion cannot be plotted on the Rumack-Matthew nomogram and cannot be used to assess the need for the antidote.

*Suzanne Doyon, MD*
*Medical Director*
*Maryland Poison Center*

## *DID YOU KNOW THAT... activated charcoal and early administration of acetylcysteine are very effective in limiting acetaminophen hepatotoxicity?*

Activated charcoal prevents the absorption of acetaminophen and should be given by EMS or in the emergency department to patients who present early after an overdose. The antidote for acetaminophen poisoning is acetylcysteine. Oral N-acetylcysteine is indicated in both early and late-presenting cases as well as chronic acetaminophen ingestions. Intravenous acetylcysteine is FDA-indicated in acute acetaminophen ingestions presenting within 8-10 hours of ingestion.

Maryland Poison Center
University of Maryland School of Pharmacy

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# President's Commentary



Frank "Butch" Henderson, P.D.
President

***Change is in the air…***
Whether you voted for it or not, it's there. The pharmacy community is positioned to respond to the challenge of health care reform. Pharmacists will be key components of a system that will be designed to promote the safe, appropriate, and correct use of medications, in order to achieve positive health outcomes and to control the overall costs incurred by the system. Sound good so far? The good news is that we have large numbers of pharmacists in the state who are already participating at this level. They have learned how to document these services, a key component of pharmacy of moving to a system that is based more on cognitive services rather than dispensing a product. I have challenged our professional development committee to continue to look for innovative programs to teach and assist pharmacists who would like to be more involved with MTM—from basic interventions such as adherence reviews and drug selection protocols to more advanced tasks such as comprehensive reviews and drug therapy management.

***Change…***
We need to encourage more pharmacists to become active in the legislative process. Grassroots efforts are necessary to ensure that our legislators understand the real issues affecting pharmacy. The current AMP based pricing model for Medicaid disincentivizes the use of generic drugs by reimbursing the pharmacy 36% on average below cost. Some pharmacies may not be able participate or may cut hours and others may close. We need Congress to fix this! Maybe we can tap into the 4 billion dollars that the pharmaceutical companies spend each year on direct-to-consumer ads. I don't know about you but I am tired of seeing these commercials. Let the professionals prescribe not the actors. (Besides, my wife still won't let me install an outdoor tub in the yard! So as far as I can tell these ads aren't very effective anyway).

***Change…***
the association suffered a great loss in the passing of Joe Kaufman, our attorney for over 50 years. Joe's contributions will be remembered and cherished by all. Joe enjoyed speaking at our meetings. You never knew what he might say but you knew that it would be passionate and from the heart from a man who truly cared about Maryland pharmacy and Maryland pharmacists. He will be missed.

***Change…***
what happened to the Kelly Building? Hopefully you were able to attend our open house earlier this year, and collect a piece of history. We are honored to be able to place items in the schools of pharmacy, and other locations, so that future pharmacists can see an important piece of the history of pharmacy in Maryland. Our new offices at Montgomery Park features many pieces from both museums as well as the library, if you come to a Board meeting you can check it out!

I look forward to the next year, and hope to see all of you at meetings. Please let me know if you have any questions or concerns, or just want to talk pharmacy, my e-mail is b.henderson@kleinsonline.com. Go green and give this journal to a friend, when you have finished, and ask them to consider becoming a member! Respectfully, Butch.

# Pharmacy Time Capsules 2009

## 1984—Twenty-five years ago

- The 50th anniversary of the APhA headquarters building on Constitution Avenue was celebrated.
- Drug Price Competition and Patent Term Restoration Act (*Waxman-Hatch)* simplifying the Abbreviated New Drug Application process and extending patent life for exclusivity lost as a consequence of FDA delays was signed into law.
- FDA approved Nicorette 2mg on January 13, 1984, for prescription use only. One of only three NDAs classified as 1-A in 1984.

## 1959—Fifty years ago

- Bill Apple became secretary of APhA replacing Robert Fischelis.
- Alaska and Hawaii become the 49th and 50th states.

## 1934—Seventy-five year ago

- North Carolina pharmacist and University of Maryland graduate, Caleb Bradham died. Bradham developed a soda drink that incorporated vanilla, essential oils, and kola nut that he named Pepsi-Cola.
- There was an open protest against the sale of grocery items in drugstores at the annual meeting of the South Dakota Pharmaceutical Association.
- A number of states still licensed pharmacy assistants allowing pharmacy assistants to operate a drugstore in the temporary absence of a registered pharmacist. Temporary defined as short as 2 consecutive hours (Indiana) to no more than one-third of the time per week that the store is open (Tennessee).

## 1909—One hundred years ago

- Founded by pharmacist Al Falkenhainer, Druggists Mutual Insurance Company (now Pharmacists Mutual) was chartered by Iowa on October 16.
- University of Tennessee moved its pharmacy program from Knoxville to Memphis.

## 1859—One hundred fifty years ago

- Chicago College of Pharmacy formed; later merged (1896) with the pharmacy program at the University of Illinois.

By: Dennis B. Worthen Lloyd Scholar, Lloyd Library and Museum, Cincinnati, OH

*One of a series contributed by the American Institute of the History of Pharmacy, a unique non-profit society dedicated to assuring that the contributions of your profession endure as a part of America's history. Membership offers the satisfaction of helping continue this work on behalf of pharmacy, and brings five or more historical publications to your door each year. To learn more, check out: www.aihp.org*

# Rx AND THE LAW

By Don R. McGuire Jr., R.Ph., J.D.

*This series, Pharmacy and the Law, is presented by Pharmacists Mutual Insurance Company and your State Pharmacy Association through Pharmacy Marketing Group, Inc., a company dedicated to providing quality products and services to the pharmacy community.*

# JURISDICTION

Because the United States has many different court systems, the law applied to your case can have a dramatic impact on the outcome. One important factor in any legal dispute is the jurisdiction. But what does that mean? Jurisdiction is defined as the power to hear and determine a case.[1] Courts can have general jurisdiction or limited jurisdiction.

General jurisdiction courts can hear and decide almost all types of cases. An example would be the district or superior court in your county. In a typical situation where a pharmacist is sued by a patient, this would be the forum where the case would be heard. However, there are other situations where this would not be true.

Pharmacies that do a significant amount of business out of state and have registered as a non-resident pharmacy with that state's board of pharmacy are probably subject to the jurisdiction of that state's courts. Long Arm Statutes have been enacted in most states. These laws allow local courts to have jurisdiction over non-resident defendants in certain circumstances. If an error occurs on a prescription sent to another state and the patient is harmed, the pharmacy could have to defend the case in that patient's locale. This can be inconvenient and expensive for the pharmacy, but it is a potential price the pharmacy would ay for doing business in that state.

Pharmacists could also end up in another state's court due to a contract which they signed. Parties to a contract may agree to a particular jurisdiction in the contract. Then in the event of a breach of that contract, the parties do not have to contest the proper jurisdiction because it has been agreed upon in advance. Pharmacies may enter into contracts with many different vendors, each of which may stipulate to a different jurisdiction. This could result in the pharmacy defending a breach of contract claim in a far away state.

Courts of limited jurisdiction are limited to hearing only certain subject matters. Examples of these would be a small claims court or a probate court. Patients could bring cases against their pharmacist in small claims court, but their ultimate recovery would be limited by the jurisdictional limit of the small claims court.

[1] Barron's Law Dictionary Second Edition; 1984; edited by Steven H. Gifis

Interestingly, Federal courts are courts of limited jurisdiction. The structure of the Federal court system parallels the structure of most state court systems. While the trial courts in state systems are courts of general jurisdiction, the Federal trial courts are not. Federal court jurisdiction is limited to two types of cases. Federal Question jurisdiction consists of cases involving disputes arising under the U.S. Constitution or the laws and treaties of the United States. The other Federal jurisdiction is Diversity jurisdiction. This occurs when the opposing parties come from different states. Therefore, it is possible that the case described above where the pharmacist sent prescriptions out of state could be brought in Federal court if the jurisdictional amount was met. Diversity jurisdiction requires the amount in controversy to exceed $75,000. Smaller cases will be relegated to the state courts even though the opponents are from different states.

In either a general or a limited jurisdictional court, the court must have both subject matter and personal jurisdiction. That is, the court must have jurisdiction over both the subject of the case and over the parties involved. Most often, courts of limited jurisdiction are limited because of the subject matter of the case. A court's jurisdiction over a person results from the person's physical presence in the state, but jurisdiction over a person can be expanded by the Long Arm Statutes previously mentioned.

If a party feels that the court doesn't have the power to hear and decide the case, the party should file a motion asserting the lack of personal or subject matter jurisdiction (or both) with the court. The judge can also rule on the subject of jurisdiction on their own initiative. If a court does not have jurisdiction, then the judge should dismiss the case from that court's docket. However, the plaintiff is then free to file the case in the proper court. A court without jurisdiction over a case cannot issue a valid decision in that case. Any judgment issued by a court without proper jurisdiction is void.

In summary, most cases involving pharmacists or pharmacies will typically be heard in their local courts. However, certain activities or contractual agreements could result in the pharmacist dealing with a case in a distant jurisdiction. The law in that jurisdiction may or may not have an impact on your case, but nonetheless the distance involved will make the case more bothersome.

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© Don R. McGuire Jr., R.Ph., J.D., is General Counsel at Pharmacists Mutual Insurance Company.

*This article discusses general principles of law and risk management. It is not intended as legal advice. Pharmacists should consult their own attorneys and insurance companies for specific advice. Pharmacists should be familiar with policies and procedures of their employers and insurance companies, and act accordingly.*

# Therapeutically Speaking...

## Cure for the Common Cold is No Child's Play

Kevin Malloy, Student Pharmacist
Donna Huynh, Pharm.D., BCPS, MA, Assistant Professor
University of Maryland School of Pharmacy

***Community pharmacists are often referred to as being on the "front line" of health care since they are the most accessible health care professional. Part of being on the front line is fielding questions from concerned parents about what is the best over-the-counter medication (OTC) for their sick child with cough and cold symptoms. According to the National Institute of Allergy and Infectious Disease, children have six to ten colds per year while adults have two to four colds per year.[1] In 2004, there were over 800 OTC cough and cold products available in the United States. This article aims to explain what recommendations can be made and what recommendations should not be made to treat cough and cold symptoms in children.***

Decongestants, antihistamines, expectorants, cough suppressants, antipyretics, and analgesics all fall under the classification of "cough and cold" with many common OTC products containing a combination of these different agents. Prior to 2008, most OTC cough and cold products for children were labeled *not* to be used in children under the age of two. On October 8, 2008, the FDA issued a statement of support in favor of the voluntary actions of the Consumer Healthcare Products Association (CHPA) to change the labels of OTC cough and cold medications to read "Do not use in children under four". In an investigation by the CDC, it was revealed that from 2004-2005 over 1,500 children under the age of two were treated in emergency departments for adverse reactions related to OTC cough and cold products. The same report noted that in 2005, three infants under six months of age died with detectable levels of pseudoephedrine, dextromethorphan and acetaminophen in their blood.[2] In 2007, 16 Maryland physicians petitioned the FDA to ban the marketing of cough and cold products to parents of children less than six years of age due to the fact that in 2004, 900 children in Maryland had accidentally overdosed on OTC products resulting in the death of four children under the age of five.[2,3] This data resulted in the voluntary label change of OTC cough and cold products to read "Do not use in children under four". Does this mean that these products are safe and effective to use in children over the age of four?

Studies demonstrating the safety and efficacy of OTC cough and cold products in the children are lacking. The American Academy of Pediatrics (AAP) released a statement about products containing codeine or dextromethorphan stating that children's dosages for these medications are extrapolated from adult data and there are no well controlled studies to support efficacy in children.[4] Additionally, cough suppression in pulmonary diseases can be dangerous and cough due to viral infections should resolve on its own within 3-8 weeks. Additionally, dextromethorphan has been shown to have adverse effects such as respiratory depression, drowsiness and behavioral disturbances. Given that doses for children are not well-established, parents run the risk of exposing their children to these side effects if they administer this medication. A study evaluating sleep quality for children taking dextromethorphan, diphenhydramine, or placebo found no significant difference between drug treatment and placebo with regards to sleep quality. In other studies, antihistamines in combination with nasal decongestants were not shown to reduce acute cough.[5] As of 2007, two studies on guaifenesin in children with cough and chest congestion had been published with one showing benefit and the other showing no significant benefit.[5,6] Overall, there has been no strong data for or against the treatment of acute cough with OTC products.[6]

A systematic review of 27 studies sought to examine the effect of antihistamines on symptoms of a common cold such as rhinnorea. The review showed no significant difference in efficacy between placebo and antihistamines regarding treatment of a cold but antihistamines were shown to cause significantly more sedation, dizziness, dry eyes, dry mouth and constipation than placebo. Some studies investigated the use of decongestants in children.[5] Overall, there were no evidence of efficacy seen in children under the age of 12 therefore these products could not be recommended for the symptomatic treatment of the common cold.[2,3]

**What recommendations CAN be made?**

Overall, there is a great deal of evidence against the use of OTC cough and cold medications in children. Regardless of what the literature says, anxious parents will continue to seek recommendations from the pharmacist to treat cough and cold symptoms in their child. So what CAN be used for coughs and colds in children?

One very important step in the process of fielding a question about pediatric self-care is to make sure you have a clear picture of why a parent is asking for a recommendation. Getting a clear picture of the symptoms being experienced by the child is crucial when making recommendations. If an infant < 3 months of age has any signs of fever, or if an infant ≥ 3 months of age has a fever greater than 101°F (38.3°C), they are not candidates for self-care and should be seen by a physician. Similarly, if a child is having difficulty breathing or appears to be in acute distress, then the child is not a candidate for self care and should go see a physician as soon as possible. If the parent expresses that their child is experiencing a cough, then it is important to find out if the child has any other conditions (e.g., asthma) that may be contributing. In the case of an acute cough, OTC medications are *not* recommended; instead the AAP and the American College of Chest Physicians (ACCP) recommend increasing fluid intake or using a cool mist humidifier in the child's room to keep the air moist.[4]

A runny nose is a common complaint among children. Data has shown that antihistamines and decongestants have questionable efficacy. One safe suggestion that can be made is the use of saline nasal spray to clear the nasal passages. Children may not enjoy the nasal spray but it should provide some symptomatic relief. If there is no pain or fever, a product containing acetaminophen or ibuprofen is unnecessary.

Children presenting with a low-grade fever have several treatment options. Acetaminophen is regarded as the first line agent in the treatment of fever in the children. If acetaminophen or ibuprofen is chosen by a parent, then it is important to counsel them on the proper product selection and dosing of the medication. There are many different formulations available with tablets, caplets, solutions and drops all available at different strengths and concentrations. It is important that parents be made aware of the maximum dosage that is appropriate for their child. Parents should also be asked to demonstrate the use of the measuring device such as oral syringes in front of a pharmacist to ensure the child is receiving the proper dose. The recommended dosing for acetaminophen in children is 10-15 mg/kg per dose no more frequently than every 4 hours. In light of the recent statements made by the FDA regarding acetaminophen toxicity it is possible that parents will express a great deal of concern using this medication over other choices such as ibuprofen. It is important to use this as an opportunity to reiterate that acetaminophen is a safe and effective medication when used properly at the appropriate dose. Ibuprofen is an acceptable medication choice as well in children over 6 months of age at 7.5-10 mg/kg per dose every 6-8 hours not to be used more than 4 times in a 24 hour period. Parents should be counseled on common side effects of ibuprofen such as nausea, vomiting, stomach pain, and black and tarry stools with extreme caution or avoidance of ibuprofen altogether in patients with renal insufficiency or a history of gastrointestinal problems. Aspirin is not recommended in children due to the risk of Reye's syndrome.

Overall, it seems that when fielding questions regarding OTC cough and cold products for children, a pharmacist may find themselves left with more questions than answers for patients. The take-home message that every pharmacist should try to convey to their concerned parents is that while cough and cold symptoms may be upsetting and bothersome to patients and parents, the uncertain efficacy and safety of cough and cold products in children appears to be far more upsetting and bothersome. Pharmacists can recommend non-pharmacological therapy in most children for complaints of acute cough and runny nose whereas problems such as fever can be appropriately dealt with using acetaminophen or ibuprofen. Navigating the cough and

cold section of a pharmacy accompanied by a sick child can be quite daunting for a parent but with the help of community pharmacists the journey should be made far easier.


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## INFLATION – STILL A DANGER FOR RETIREMENT INVESTORS

The first steps in planning for the retirement years are to survey your current financial situation and define your goals. Be sure to consider your wishes for:

- Growth of capital
- Income
- Tax savings
- Safety

**Inflation: still a danger**

Many people say, "My goal is not to lose my money." But even this goal can be misleading. If your assets are earning two percent in a very "safe" place while the inflation rate is three percent, your purchasing power is being eroded at about one percent per year. To add insult to injury, you have to pay tax on the earnings—so your purchasing power is actually being eroded faster. Over the years, an expenditure like replacing a roof or going on a trip becomes a major financial undertaking.

In recent years, inflation has not been the obvious menace that it was in the late 1970s and early 1980s. According to the Bureau of Labor Statistics, the average rate of inflation from 1985 to 2005 was 3.0%. This "low-grade" inflation can lull investors into dismissing inflation as unimportant.

But at that rate, for every $10,000 of income you need today, you'd need $13,400 ten years from now and $18,000 twenty years from now. As prices continue to rise each year, your purchasing power is being eroded. And this doesn't take into account the damage that can be done by "bracket creep"—finding yourself in a higher tax bracket because of the rising *number* of dollars you take in, despite their lower *value*.

To offset the effects of inflation on your portfolio, you must ensure that the total return (growth plus income) of your investments meets or beats the rate of inflation—adjusted for any movement to a higher tax bracket. Your financial advisor can help you establish your investment goals and design a portfolio to balance all your investment needs.

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continuing education for pharmacists

Volume XXVI, No. 11

# Ischemic Stroke: Prevention and Treatment

*Thomas A. Gossel, R.Ph., Ph.D., Professor Emeritus, Ohio Northern University, Ada, Ohio and*
*J. Richard Wuest, R.Ph., PharmD, Professor Emeritus, University of Cincinnati, Cincinnati, Ohio*

**Goal.** The goal of this lesson is to discuss ischemic stroke (cerebrovascular accident) with focus on its clinical characteristics and treatment.

**Objectives.** At the conclusion of this lesson, successful participants should be able to:

1. recognize epidemiologic information and clinical characteristics relevant to ischemic stroke;
2. identify symptomatology that characterizes ischemic stroke and the principles that govern clinical confirmation and management; and
3. select from a list specific therapeutic measures that are reported to modify signs and symptoms of ischemic stroke.

## Background

Worldwide, 5.5 million people die each year as a result of stroke. Another 15 million survive, but are disabled. In the United States, the incidence is at pandemic proportions; 700,000 individuals will be stricken annually, with 200,000 of these events being a recurrent event. Each year, about 46,000 more women than men in the United States experience a stroke. When considered separately from other cardiovascular disease, stroke ranks third among all causes of death in this country, behind heart disease and cancer. The mean lifetime direct cost of ischemic stroke per individual in the United States is estimated to be $140,048.



Gossel



Wuest

## Pathogenesis of Stroke

Stroke can be caused by localized obstruction of the blood supply into an area of the brain due to its mechanical blockage in an artery (ischemic stroke), or by blood escaping from an artery within the brain (hemorrhagic stroke). It encompasses pathology in both the cerebrovascular and the cardiovascular circulations.

Cerebral ischemia resulting from large-vessel atherosclerosis (the most common cause of ischemic stroke) and coronary ischemia share common mechanisms including plaque accumulation within vessel walls, erosion and rupture, inflammation, apoptosis (natural or programmed cell death) and thrombus (clot) formation. Advancing age is a risk factor. Stroke prevalence varies by gender and race (Table 1). Studies have noted relationships between initial stroke, vascular risk factors (e.g., hypertension, diabetes, hyperlipidemia), and lifestyle risk (e.g., smoking, alcohol use, obesity, lack of physical activity). Factors correlating with recurrent stroke include large artery atherosclerosis, previous multiple strokes, disability after stroke and diabetes mellitus. Ischemic strokes are reported in American Heart Association statistics to account for 87 percent of all strokes.

Following ischemia-induced oxygen deprivation, some neurons die within minutes to cause irreversible brain injury. Surrounding the area of necrosis (the infarct) is tissue called the penumbra in which the blood supply is marginally sufficient to maintain minimal cellular activity. In the absence of sufficient blood supplied from adjacent arterioles (reperfusion) or with additional injury, a time-related death occurs to the penumbra and it will be incorporated into the infarct.

**Hypertension.** In humans, changes in blood pressure follow a reproducible pattern over 24 hours that includes a rapid early-morning surge associated with awakening. This response coincides with increased risk for stroke. In a meta-analysis of 31 published reports describing the circadian timing of 11,816 strokes, most events occurred between 6:00 a.m. and 12:00 noon. A similar variation was noted for different subtypes of stroke: ischemic (n=8,250), hemorrhagic (n=1,801) and transient ischemic attack (TIA) (n=405). It is logical to reason that antihypertensive agents and their dosing schedules should be selected that provide

**Table 1**
**Prevalence and annual incidence of stroke by gender and race in the United States**

| Population | Prevalence (%) | Incidence* |
|---|---|---|
| Total | 2.6 | 700,000 |
| Total men | 2.5 | 327,000 |
| Total women | 2.6 | 373,000 |
| White men | 2.3 | 277,000 |
| White women | 2.6 | 312,000 |
| African-American men | 4.0 | 50,000 |
| African-American women | 3.9 | 61,000 |
| Mexican-American men | 2.6 | ----- |
| Mexican-American women | 1.8 | ----- |
| Hispanic or Latino | 2.2 | ----- |
| Asian | 1.8 | ----- |
| American Indian/ Alaskan Native | 3.1 | ----- |

*Includes new and recurrent strokes

Adapted from Dickerson LM, Carek PJ, Quattlebaum RG. *Am Fam Physician.* 2007;76:282.

adequate blood pressure control during the early morning hours.

**The Role of Cholesterol.** The linear relationship between serum cholesterol concentration and cardiovascular disease is more clear than that between serum cholesterol concentration and stroke. Most large epidemiologic studies have not separated the various types of stroke in terms of etiology, but have grouped heterogeneous mechanisms into the single category of ischemic stroke, weakening the likelihood of finding a clear association. One investigation reported that serum cholesterol levels higher than 280 mg/dL were associated with increased risk for death from ischemic stroke while concentrations less than 160 mg/dL were associated with increased risk for hemorrhagic stroke. Other studies demonstrated that cholesterol levels greater than 300 mg/dL were associated with increased risk for non-hemorrhagic stroke. The correlation between cholesterol level and stroke, while hazy, nevertheless associates lipid disorders to the pathogenesis of atherosclerosis in both cardiovascular and cerebrovascular disease and, as mentioned earlier, is noted as the primary cause of ischemic stroke.

## Transient Ischemic Attack

Transient ischemic attack (TIA) is common with 300,000 events occurring annually in the United States. A TIA ("mini-stroke," "small-stroke") is experienced as a temporary focal (localized) neurologic deficit. The most common symptom is sudden onset of muscular weakness affecting one side of the body (hemiparesis). A sensation of numbness on one side of the body (hemiparesthesia), inability to speak clearly and/or imbalance, along with blurred vision or blindness in one eye and double vision (diplopia) are others. The focal and temporary nature of symptoms differentiates TIA from ischemic stroke. Lack of clear distinction between these afflictions with regard to other symptoms has led to the emphasis of a single criterion: TIA symptoms last less than 24 hours, typically only a few minutes. This short duration, followed by complete recovery and absence of neurologic deficit on examination, makes TIA particularly challenging.

Numerous prospective, observational studies have shown that following TIA, patients are at extremely high risk for a full-blown stroke. In one study of more than 1,700 patients who appeared in an emergency department with TIA, the 90-day risk of stroke was 10.5 percent. This was a 50-fold greater risk than expected for an age-matched cohort of persons without TIA. The risk of stroke was front-ended with over half of the secondary events appearing within the first two days. Twenty-one percent of the stroke victims died and another 64 percent were disabled. From these data it was concluded that for every 100 patients with TIA, 2.2 would die and 6.7 would be disabled within three months as a result of stroke.

The most urgent need for a patient with symptoms suggesting TIA or stroke is to identify the nature of the event, whether ischemic or hemorrhagic. Even though symptoms of TIA may have abated before initial consultation, a thorough history and examination can illuminate whether the patient has experienced similar events previously. It can also yield a preliminary assessment of risk factors and possible etiology.

Since symptoms are transient and may have nonischemic causes such as seizure and syncope, and since physicians rarely actually observe a patient during a TIA, it is often difficult if not impossible to confirm a diagnosis on the spot. Agreement between independent observers on TIA diagnosis is reported to be poor even among neurologists.

## Atrial Fibrillation

Atrial fibrillation is a signature disorder of aging, with a prevalence of about 5 percent in persons aged 65 years and older and approximately 10 percent of those over the age of 80. With prevalence increasing, partly because of an aging population, it is projected that by year 2050 there will be an estimated 5.6 million people in the United States with atrial fibrillation, about half of them being over 80 years of age. Atrial fibrillation increases the risk of ischemic stroke by approximately five-fold and is the cause of an estimated 15 percent of all ischemic strokes in the United States. This proportion is even higher, approxi-

mately 24 percent, in persons aged 80 to 89 years. The prevention of atrial fibrillation-related stroke is an important public health concern since strokes occurring from atrial fibrillation result in higher mortality and disability.

Warfarin is highly effective in preventing atrial fibrillation-related stroke, reducing stroke risk by about 68 percent and mortality by 33 percent, and it also appears to prevent the most severe type of ischemic stroke. However, because elderly patients have both the highest risk for stroke without warfarin and the highest risk for hemorrhage with it, maximizing anticoagulation therapy while minimizing toxicity is a central challenge for its use in these persons. The drug's narrow therapeutic window and associated hemorrhagic toxicity can make anticoagulation management difficult. Optimal anticoagulation intensity, measured by the International Normalized Ratio (INR), is between 2.0 and 3.0. Low fixed-dose warfarin is ineffective in preventing strokes, although clinicians may settle for lower INRs in older patients. INR values under 2.0 significantly increase the risk for stroke. Older patients are less likely than younger ones to receive anticoagulation therapy and more likely to receive insufficient doses.

Aspirin provides some protection from stroke in persons for whom warfarin is contraindicated. Although aspirin reduces stroke risk by about 21 percent and has fewer hemorrhagic complications than warfarin, a randomized trial comparing the two treatments in persons between the ages of 80 and 90 years showed that more patients discontinued aspirin therapy compared with warfarin, mostly due to gastrointestinal side effects.

The warfarin arm of the Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE-W) study showed warfarin to be superior to combined clopidogrel (Plavix) plus aspirin with similar rates of hemorrhagic complications. Investigations into other antithrombotic agents continue; for now however, warfarin remains the most effective drug to prevent stroke in patients with atrial fibrillation.

## Symptoms and Confirmation of Acute Ischemic Stroke

Acute stroke is characterized by the sudden onset of a focal neurologic deficit, although some patients experience a stepwise or gradual progression of symptoms. Common deficits include impaired speech (dysphasia), defective vision or blindness in half of the visual field (hemianopia), weakness, ataxia and sensory loss. Signs and symptoms are typically unilateral, and consciousness is generally normal or only slightly impaired. Persistence of any neurological deficit beyond two hours, even if the patient subsequently recovers, nearly always is accompanied by some degree of tissue destruction.

Ischemic stroke cannot be distinguished with certainty from intracerebral hemorrhage on the basis of signs and symptoms alone. In all patients with suspected stroke, computed tomography (CT, CAT scan) or magnetic resonance imaging (MRI) of the brain is necessary. Both CT and MRI have a high sensitivity for acute intracranial hemorrhage, but MRI has a much higher sensitivity than CT for acute ischemic changes, especially in the first hours after an ischemic stroke.

## Prevention and Treatment

Patients with a history of ischemic stroke and/or TIA are high risk for subsequent cerebrovascular and cardiovascular events. Current guidelines for prevention support the aggressive modification of risk factors, including smoking cessation, reduction in alcohol consumption for heavy drinkers, weight reduction, antihypertensive therapy and rigorous control of blood glucose. Four antiplatelet agents have been shown to reduce the risk for recurrent ischemic stroke: aspirin, ticlopidine, clopidogrel, and dipyridamole. These are discussed subsequently.

**Treatment of Acute Ischemic Stroke.** Responses from numerous clinical trials are in agreement that patients who receive care in a primary stroke center are more likely to survive, regain independence and return home than are those who do not receive such specialized care. Once ischemic stroke has been confirmed, the next step is to determine whether the patient might be a candidate for thrombolysis therapy. Acute thrombolysis is the most promising approach to treat acute stroke.

**Intravenous Thrombolysis with a Recombinant Tissue Plasminogen Activator (rt-PA).** Despite FDA approval more than a decade ago and the fact that alteplase (Activase) is currently the only approved rt-PA treatment for this condition, alteplase reportedly remains underused in the United States. In one study, 69 percent of hospitals did not use thrombolysis at all. In hospitals that did (mostly those with a high volume of stroke patients), only 1 percent of stroke patients received thrombolysis. Other estimates are that 6 to 8 percent of ischemic stroke patients are potentially eligible for rt-PA based on published criteria, but only 3 to 4 percent receive it.

The National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator (NINDS rt-PA) Stroke Study was a multicenter, randomized trial that demonstrated efficacy of treatment with intravenous alteplase started within three hours after onset of symptoms. Thirty-one to 50 percent of 624 patients receiving alteplase at a dose of 0.9 mg/kg of body weight, 10 percent of the dose given as a bolus and the remainder infused over one hour at a maximum total dose of 90 mg, had a favorable neurologic or functional outcome at three months, compared with 20 to 38 percent of patients given placebo. Symptomatic intracerebral hemorrhage occurred in 6.5 percent of patients receiving intravenous

rt-PA and in 0.6 percent of controls.

Intracerebral hemorrhage following thrombolysis is higher in patients with increased age and those with more severe strokes. Similar concerns have been voiced about the efficacy and safety of routinely using rt-PA in patients with early ischemic changes on CT. Further analysis of data from the NINDS rt-PA Stroke Study showed that in the first three hours after onset of symptoms, the appearance of ischemic changes on CT was not an independent predictor of increased risk of symptomatic intracerebral hemorrhage or other adverse outcomes following treatment with rt-PA. Several studies have concluded that intravenous thrombolysis with rt-PA can be used in the community hospital setting with efficacy and safety similar to that found in the randomized trials. The effect of aspirin in combination with rt-PA is unknown, so it is recommended that aspirin be withheld for 24 hours in patients treated with intravenous thrombolysis. Neither dipyridamole nor clopidogrel have been tested in randomized trials in the acute phase of ischemic stroke.

**Anticoagulants.** A meta-analysis of six randomized trials involving 21,966 patients found no evidence that anticoagulants (unfractionated heparin, low-molecular-weight heparins, heparinoids, thrombin inhibitors, or oral anticoagulants) administered during the acute phase of stroke improve functional outcomes. While their use does not improve overall functional outcomes, subcutaneously administered low-dose unfractionated heparin or low-molecular-weight heparin has been recommended in patients at high risk for deep venous thrombosis, such as those who are immobile. The use of heparin in patients with ischemic stroke, even progressing stroke, remains controversial.

**HMG-Co A Reductase Inhibitors.** These drugs (also called "statins") reduce stroke risk in persons with hyperlipidemia and are a powerful tool in stroke prevention. Non-statin lipid-lowering agents are not associated with decreased risk. The mechanism for statins is probably multifactorial. Reducing LDL-cholesterol levels is a benefit, but other actions may also be at play. These include effects on endothelial function, cell proliferation, inflammatory response, immunologic reactions, platelet function, and lipid oxidation. Statins have also been shown to prevent atrial fibrillation in patients in a number of different circumstances. One possible explanation may be that they reduce inflammation since markers such as C-reactive protein, which is increased in atrial fibrillation, are reduced by high doses of statins. Statins may also have independent neuroprotective effects since their use is associated with improved outcomes and functional capacity in patients who have experienced ischemic strokes.

## Secondary Stroke Prevention

Recurrent stroke prevention is a high public health priority due to resultant morbidity and mortality, as well as the healthcare costs associated with disability. The majority of strokes in the United States are noncardioembolic ischemic events, so antiplatelet agents are the recommended first-line therapy for secondary stroke prevention.

**Aspirin.** Patients with a history of ischemic stroke treated with aspirin have a lower risk of stroke and death, compared with placebo. Both low-dose (50 to 166 mg/day) and high-dose (325 mg/day) regimens are similarly effective in preventing vascular events. Higher doses are associated with more gastrointestinal side effects and bleeding episodes. Specifically, patients receiving more than 200 mg/day for at least one month have more gastrointestinal bleeding, fatal or life-threatening bleeding and total bleeding episodes compared with persons receiving less than 100 mg/day. The overall risk for major bleeding associated with aspirin (75 to 500 mg/day) is small.

**Clopidogrel.** Clopidogrel (Plavix) is approved for prevention of recurrent vascular events (MI, stroke, vascular death). In one randomized controlled trial, persons with recent ischemic stroke, MI or symptomatic peripheral arterial disease received clopidogrel (75 mg) or aspirin (325 mg) daily for two years. There was a statistically significant difference in effectiveness (although of borderline clinical significance) with clopidogrel compared with aspirin (5.32 vs. 5.83 percent risk of ischemic events).

Clopidogrel has been studied in combination with aspirin for prevention of recurrent stroke; however, the combination therapy is not recommended in patients with a history of stroke. In one trial, more than 7,000 patients with previous stroke received clopidogrel (75 mg) plus aspirin (325 mg) or clopidogrel alone for 18 months. Combination therapy was not superior to clopidogrel monotherapy in preventing secondary ischemic stroke, MI, vascular death or rehospitalization for ischemic events. The combination regimen did increase the risk of life-threatening bleeding and major bleeding.

**Dipyridamole and Aspirin.** Extended-release dipyridamole and aspirin are available in a combination product (Aggrenox) approved for prevention of recurrent stroke. In one trial, 6,602 patients receiving dipyridamole (200 mg twice daily) plus aspirin (25 mg twice daily) experienced a lower risk of ischemic stroke and TIA over the two-year period compared with aspirin alone. Combination therapy did not increase the risk of major or minor bleeding.

**Ticlopidine.** In various studies comparing ticlopidine (Ticlid) with aspirin, the antiplatelet has shown both greater and lesser activity than aspirin in reduction of risk for secondary stroke. Ticlopidine is not typically chosen for first-line use because it carries a small risk for severe neutropenia and is associated with a risk of thrombotic thrombocytopenia purpura. This is a rapidly fatal or occasionally protracted disease due

to formation of fibrin or platelet clots in arterioles and capillaries of many organs.

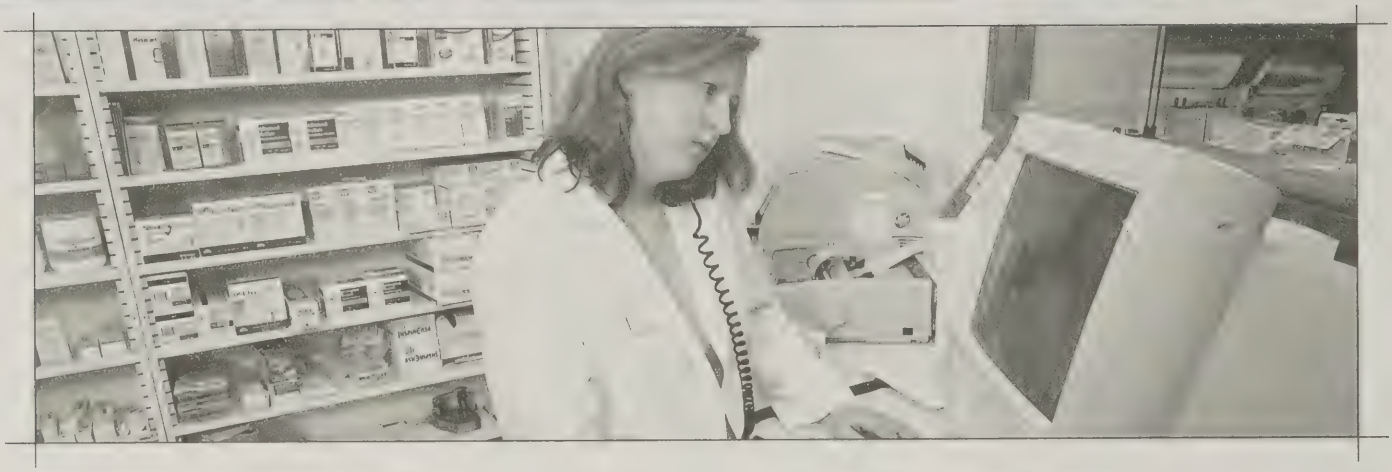
**Risk Factor Reduction in Persons with Cerebrovascular Disease.** The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) recommends maintaining a blood pressure goal of less than 140/90 mmHg. The American Heart Association/American Stroke Association guidelines recommends slowly reducing the blood pressure to goal level. These guidelines state that hypercholesterolemia should be managed according to National Cholesterol Education Panel guidelines. Statins should be used to achieve an LDL-cholesterol level under 100 mg/dL, or less than 70 mg/dL for patients with multiple risk factors. Other lifestyle recommendations include smoking cessation with reduction or elimination of alcohol consumption. Patients who are heavy drinkers (more than five drinks/day) should eliminate or reduce their consumption; light to moderate intake (fewer than two drinks/day for men and one/day for nonpregnant women) may be considered. For weight reduction to a goal body mass index under 25 $kg/m^2$ and waist circumference less than 35 inches for women and less than 40 inches for men, patients should be encouraged to engage in physical activity for at least 30 minutes most days of the week.

## Summary and Conclusions

Atrial fibrillation is a common affliction of older adults and a major risk factor for stroke. Its management is directed at preventing thromboembolism with warfarin, as well as controlling the heart rate and rhythm. Regardless of extent or duration of acute effects, TIA is a prodrome (warning sign) for ischemic stroke and carries the risk for secondary stroke comparable to that associated with ischemic stroke. Pharmacologic and nonpharmacologic interventions aimed at reducing the risk of secondary stroke should, therefore, be initiated as soon as possible after the initial event.

The content of this lesson was developed by the Ohio Pharmacists Foundation, UPN: 129-000-08-011-H01-P. Participants should not seek credit for duplicate content.

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# Continuing Education Quiz

This month's questions are taken from the article on "Ischemic Stroke: Prevention and Treatment". Circle your answers to the following questions and mail the entire page to Maryland Pharmacist CE, 1800 Washington Blvd., Suite 333, Baltimore, MD 21230-1701. There is no charge for this quiz for MPhA members (non-members $10.00). The completed quiz for this issue must be received by 11/15/2011. A continuing education certificate for one and one-half contact hours (0.15 CEUs) will be mailed to you within six to eight weeks. Please type or print clearly.
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1. The most common cause of ischemic stroke is:
   a. deep vein thrombosis.
   b. large-vessel atherosclerosis.
   c. myocardial infarction.
   d. variant angina.

2. The tissue surrounding the area of necrosis following ischemia-induced cell death due to oxygen deprivation is called the:
   a. thrombus.
   b. tamponade.
   c. penumbra.
   d. plaque.

3. A meta-analysis of 31 published reports found that most strokes occur between:
   a. 12 noon and 6 p.m.
   b. 6 p.m. and 12 midnight.
   c. 12 midnight and 6 a.m.
   d. 6 a.m. and 12 noon.

4. The linear relationship between serum cholesterol concentration and cardiovascular disease is:
   a. more clear than that between serum cholesterol concentration and stroke.
   b. less clear than that between serum cholesterol concentration and stroke.

5. The most urgent need for a patient with symptoms suggesting TIA or stroke is to identify the:
   a. nature of the event.
   b. patient's blood type.
   c. renal perfusion rate.
   d. serum cholesterol levels.

6. The most effective drug to use to prevent stoke in patients with atrial fibrillation is:
   a. aspirin.
   b. digoxin.
   c. heparin.
   d. warfarin.

7. A patient with dysphasia is experiencing impaired:
   a. body movements.
   b. breathing.
   c. speech.
   d. swallowing.

8. The effect of aspirin in combination with rt-PA is best described as:
   a. effective.
   b. unknown.
   c. ineffective.

9. All of the following are true EXCEPT:
   a. the use of heparin in patients with ischemic stroke, even progressing stroke, remains controversial.
   b. HMG-CoA reductase inhibitors reduce stroke risk in persons with hyperlipidemia.
   c. patients with a history of ischemic stroke treated with aspirin have a lower risk of stroke and death, compared with placebo.
   d. combination therapy with clopidogrel monotherapy in preventing secondary ischemic stroke.

10. In patients with multiple risk factors, the National Cholesterol Education Panel guidelines state that statins should be used to achieve an LDL-cholesterol level under:
   a. 70 mg/dL.
   b. 60 mg/dL.
   c. 50 mg/dL.
   d. 40 mg/dL.

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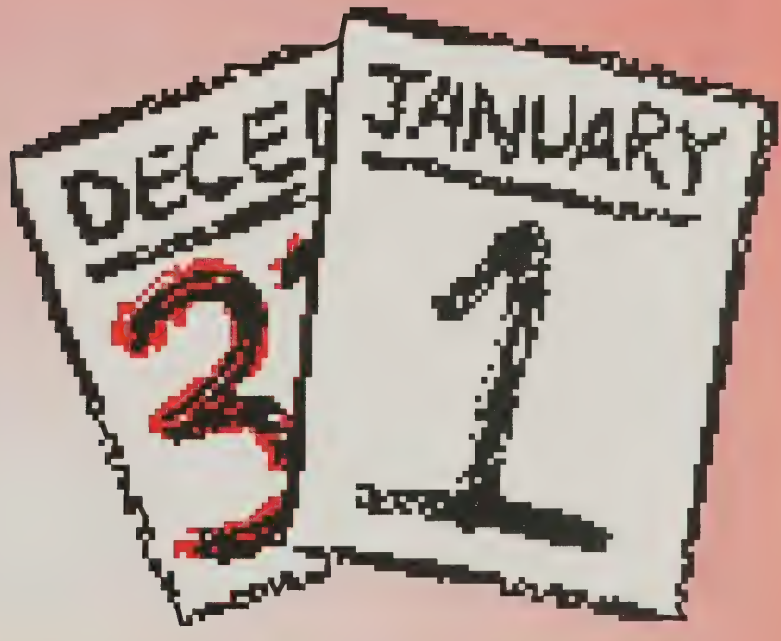
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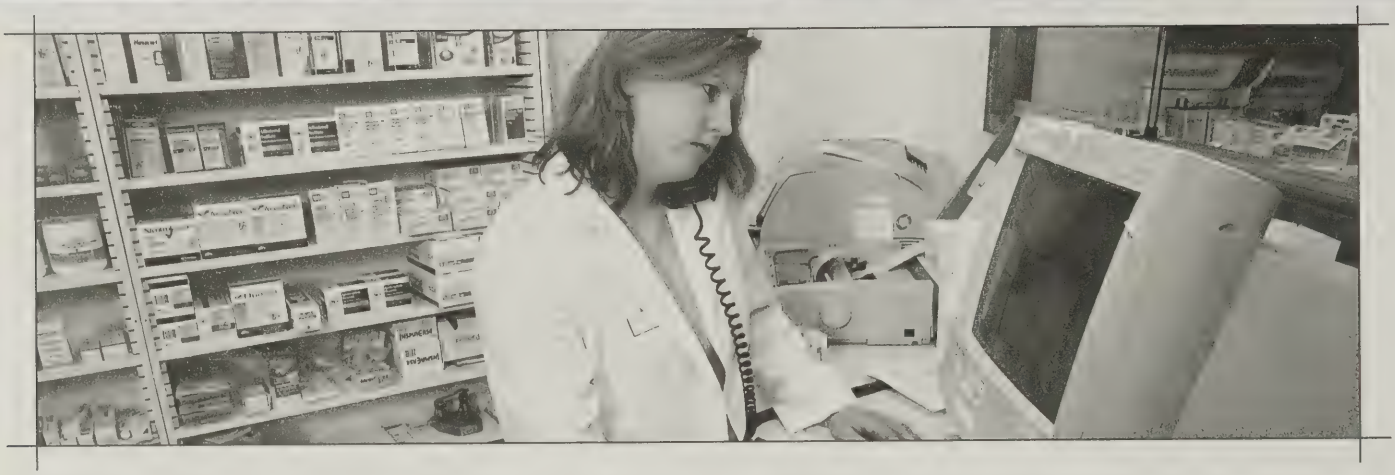

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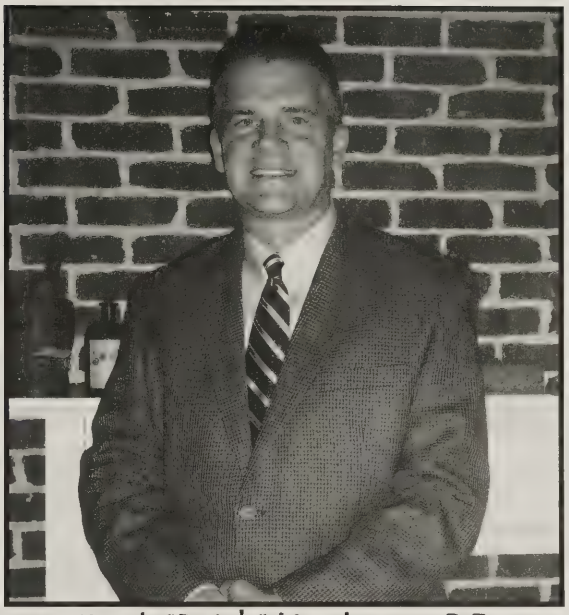
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# Presidents Message

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Today's hot topic is health care reform and by the time this article is printed, there will probably be legislation in place. Of interest to us is how these policies will relate to pharmacists and the practice of pharmacy. The goals at this time are to improve patient outcomes and to reduce overall healthcare costs, while focusing on availability and affordability. As we all know, pharmacists are positioned to be key players in this "new" health care system, especially with our advanced training and knowledge of medications, along with our existing availability and proximity to our patients.

MPhA will continue to encourage and assist pharmacists in becoming more involved in the relevant MTM services that are a part of this plan. Our professional development committee is seeking innovative programs to facilitate the training of pharmacists and encouraging participation in these programs. One of MPhA's recent initiatives has been to partner more fully with University of Maryland School of Pharmacy in the Maryland P3 program. We are committed to the success of this innovative program, as well as the future development and expansion of the pharmacist network. We will need more pharmacists to become involved, which is why I am asking you to "step up". We will need your help to succeed. Please consider becoming trained to be a part of the P3 network, and consider following two patients to get started. You may contact the MPhA office, or our partner, the University of Maryland School of Pharmacy, for more information.

The other event coming up is Legislative Day, Thursday, February 18th. To ease any trepidations you may have and to prepare you for your visit we will be hosting an educational program on Thursday, February 11th., at Montgomery Park. Legislative Day is a unique opportunity to be heard in Annapolis. Each member should consider attending this event . We will do the work for you in regard to scheduling appointments and providing information on the key bills and issues; you just need to show up! Every year we have a large representation of student pharmacists, but not enough practicing pharmacists. We need your help to get our points across, as well as to continue to create the influential relationships needed to ensure fair and reasonable policies that promote our profession. Some of the exciting issues that may be discussed this year are: disposal/take-back programs, CLIA-waivers, electronic CDS monitoring, expanded immunization opportunities, therapy management (collaborative practice), mail order prescriptions, medical marijuana... If any of these topics interest you, or you have some ideas of your own, it's time to step up! Please join us and thanks for your participation!

Respectfully, Butch

P.S. Look for the Legislative Day registration form on our web site-www.marylandpharmacist.org

# From the Editor:

Howard Schiff, P.D.

I have been asked several times how I felt about leaving the Kelly Building. Honestly, I must say I have mixed emotions. Our home for 57 years had its beauty. Kelly was in the middle of the University of Maryland campus, convenient to the School of Pharmacy and to downtown visitors. Built in the early 50s in a colonial style upon the donations of Maryland pharmacists under the leader ship of H.A.B. Dunning, the Kelly Building and the B. Olive Cole museum it housed were the "roses among the thorns." The thorns were the skyscrapers of the University of Maryland Medical System (UMMS) and the University of Maryland Baltimore.

MPhA had a 99 year lease at a dollar a year. UMMS had tried to buy (or bully) us out in the late 90s. The negotiations were contentious, rancorous and eventually collapsed. Members contributed money to remodel the building with the idea we would stay unless we "received an offer we couldn't refuse." The building and museum were rededicated in February, 2003. It was one of the best pharmacy museums in the nation with the first reaction to visitors to the lower level being a "Wow."

On the other hand, it was a 57 year old building with all the problems that a building of that age entails. The plumbing was a mess; it was difficult to tell old electrical wiring from live wiring. The lower level museum was 20 steps down and not compliant with federal disability regulations. Even, after the roof was replaced, we had occasional leaks. We were in front of the Shock Trauma Center and the Emergency Room and subject to constant sirens wailing and helicopters overhead.

We were approached by UMMS again in late 2007. Negotiations were much more cordial. We were able to get our own "bully" lawyer and negotiated the sale of our leasehold interest for an amount that, hopefully, will fund us for a long, long time.

Some of us were invited to the demolition ceremony of the Kelly Building on June 11. Not knowing whether MPhA representatives would really be welcome, we approached the occasion with some trepidation. Although we were not mentioned publicly, we were received cordially by members of the UMMS Board of Visitors. The Kelly Building will be replaced by an extension of the Shock Trauma Center. It was said that their current site is handling more than twice the population for which it was built.

Now MPhA enters a new era. Much of the 1890s part of the museum is on permanent loan to the University of Maryland School of Pharmacy for display when their new pharmacy hall is completed. Our new quarters in Montgomery Park are clean, convenient, provide sufficient space for meetings and displays, and are easy to maintain. We are still in the process of setting up displays of many of our artifacts. A decision will have to be made during the lease period to stay, buy or lease somewhere else.

# Rx AND THE LAW

By Allison Seiwert
and Don. R. McGuire Jr., R.Ph., J.D.

This series, **Pharmacy and the Law**, is presented by Pharmacists Mutual Insurance Company and your State Pharmacy Association through Pharmacy Marketing Group, Inc., a company dedicated to providing quality products and services to the pharmacy community.

## IMPACT OF STATE PRESCRIPTION DRUG MONITORING PROGRAMS

**Overview of Programs**

Prescription drug monitoring programs are helping states address prescription drug abuse, addiction and diversion. As of July 2009, a total of forty states have laws allowing for a prescription drug monitoring program (PDMP)[1]. Thirty-three states have PDMPs in place and six more have legislation enacted but are not yet operational. Washington's program has been suspended due to lack of funding. PDMPs are not a new idea; Texas began collecting data in July 1982 for Schedule II prescriptions and recently expanded the program to also cover Schedules III, IV and V. Pennsylvania passed legislation in 1972, but the program was not operational until 2002[2]. PDMPs gather information that may include: patient name, date of birth, address; drug name, strength, and quantity; doctor name and DEA; and other prescription information, date written, refills, and day supply[3].

States vary in the information gathered as well as the drugs monitored. Thirty-six states have the authority to monitor Schedule II, III and IV prescriptions. Twenty states also monitor Schedule V substances[1]. Nine states are allowed to monitor non-controlled substances (drugs of concern or have demonstrated a potential for abuse). For example, Ohio, Washington and North Dakota have authority to monitor drugs containing tramadol or carisoprodol[1].

A major goal of PDMPs is to support legitimate use of prescriptions while minimizing illicit use. The information obtained by the PDMP is accessible to prescribers and dispensers. However, there is little guidance about what a practitioner should do with the information at hand. It's up to the individual practitioner to utilize the PDMP to ensure legitimate medical use of controlled substance prescriptions.

Some state programs will notify prescribers and/or dispensers about patients receiving multiple prescriptions in the same class from multiple prescribers. In sixteen states, the PDMP laws do not require the practitioners to utilize this information. These states include: Alabama, Alaska, Arizona, Florida, Idaho, Illinois, Indiana, Iowa, Kansas, Minnesota, North Dakota, Ohio, Oklahoma, Oregon, South Carolina and Wyoming. However, not all of the states protect practitioners from civil liability if they don't use the information in the program. Of the sixteen states, Alabama and Wyoming do not provide civil immunity. Idaho and Illinois provide protection when information is accessed and used negligently but do not provide immunity for failing to access the program at all. Indiana's statute does not specifically include dispensers in the immunity provisions. Prescribers are encouraged to use data provided by PDMP in order to optimize appropriate use. Nevada mandates review by

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prescribers under certain circumstances to assess the medical necessity of a prescription[4].

In summary, PDMP are in place in the majority of states across the US. The programs vary based on type information gathered and how it's used. Overall, the goal is the same: reduce drug abuse by compiling data into a single source accessible to prescribers and dispensers. The following case highlights how several pharmacies failed to use information provided by Nevada's PDMP. The district court dismissed the pharmacies from the case, but the plaintiff has appealed to the Nevada Supreme Court for further review.

**Nevada Case**

The Nevada Supreme Court is expected to rule by the end of the year on whether seven chain pharmacy owners and one independent owner were rightfully dismissed from the civil case, Sanchez v. Wal-Mart Stores, et al[5]. The case arises from a June 2004 car accident caused by Patricia Copening. While under the influence of prescription medications, she was driving along a busy Nevada highway. The accident killed one man, Greogry Sanchez, Jr. and injured another, Robert Martinez. Prior to the accident, in June 2003, the Nevada controlled substance task force sent letters to 14 Las Vegas area pharmacies informing them that Copening may be abusing drugs. It is not clear at this time what information was contained in the letter, but there is no documentation to show that it was considered prior to dispensing future prescriptions to the patient. Yet she continued to receive multiple prescriptions for hydrocodone-acetaminophen and carisoprodol. One year later, the accident occurred and she was found to have hydrocodone in her system. She appeared confused and the police found prescription bottles and loose tablets in the vehicle. She served nine months in jail after pleading guilty to reckless driving. A civil case was filed by the Sanchez family, Mr. Martinez and his family against Copening, the doctors prescribing for her, and the pharmacies. The district court dismissed the pharmacies as Nevada law does not specify the action to be taken by the pharmacies when notified of a potential drug abuser. Therefore, the district court found the pharmacies did not have a legal obligation to refuse to fill Copening's prescriptions. This case of first impression may have an impact on how practitioners use information obtained from PDMPs.

The question of the case becomes: did the pharmacies have a duty to act upon information received from the task force warning of a patient's potential drug abuse? Time will tell. An update will follow when the Nevada Supreme Court releases its opinion.

© Allison Seiwert and Don R. McGuire. Allison is a PharmD Candidate 2010, JD Candidate 2012 from Drake University on rotation at Pharmacists Mutual Insurance Company. Don R. McGuire Jr., R.Ph., J.D., is General Counsel at Pharmacists Mutual Insurance Company.

*This article discusses general principles of law and risk management. It is not intended as legal advice. Pharmacists should consult their own attorneys and insurance companies for specific advice. Pharmacists should be familiar with policies and procedures of their employers and insurance companies, and act accordingly.*

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November 2009

# Ingestion of Isopropanol

Isopropanol (also known as isopropyl alcohol) is a common household chemical found in cleaning solutions, disinfectants, and topical preparations. It is most often available in homes as a component of rubbing alcohol at concentrations of 70-99%, with 70% being most common. Due to its low cost and availability, isopropanol is sometimes ingested as a substitute for ethanol. Isopropanol is absorbed rapidly and completely after ingestion and may also be absorbed via inhalation or transdermally, especially in children. It has similar inebriating properties as other alcohols, producing greater CNS depressant effects than ethanol at comparable concentrations.

It is important to differentiate isopropanol ingestion from ingestion of other toxic alcohols, such as ethylene glycol (antifreeze) or methanol (windshield washer fluid), because isopropanol poisoning is treated differently. A distinguishing clinical feature is the presence of a fruity odor on the breath of an isopropanol poisoned patient. This is a result of the production of acetone as the isopropanol is metabolized in the liver. Unlike other toxic alcohols, isopropanol does not cause metabolic acidosis or elevated anion gap, but does cause ketosis. Isopropanol is osmotically active, so an osmolal gap may be observed but should not be used to confirm isopropanol poisoning.

Clinical effects of isopropanol are similar to those of ethanol and include vomiting, abdominal pain, confusion, stupor, hypotension, and hypoglycemia. Most patients recover within 24 hours. Treatment is symptomatic and supportive care (intubation if necessary and IV fluids to correct hypotension). Activated charcoal is not useful for decontamination since alcohols are absorbed rapidly and are not highly bound by charcoal. Isopropyl alcohol is dialyzable, but hemodialysis is rarely required. Inhibition of metabolism with fomepizole is not recommended; isopropanol is more toxic than its metabolite (acetone), and fomepizole extends isopropanol's half-life from about 3 hours to as long as 27 hours. Patients in the emergency department who are known to have ingested isopropanol and are asymptomatic after 2 hours may be discharged, as serum concentrations peak rapidly after ingestion, often before presentation.

*Rick Brown*
*PharmD Candidate*
*University of Maryland School of Pharmacy*

## *DID YOU KNOW THAT… isopropyl alcohol ingestion can falsely elevate the serum creatinine?*

There have been reports of "pseudo"-renal failure in patients who ingest isopropyl alcohol. A false elevation in serum creatinine can occur due to acetone interfering with the creatinine colorimetric assay. Using an enzymatic assay, such as that used in a blood gas analyzer, instead of the colorimetric assay will avoid the acetone interference and give a rapid and accurate measure of the patient's serum creatinine.

Maryland Poison Center
University of Maryland School of Pharmacy

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From the April 1953 issue of the...

Maryland Pharmacist

**LETTER TO THE EDITOR**

Baltimore, Maryland

Dear Joe:

The pricing of prescriptions always seems an everlasting problem. As far back as 1872, a pricing schedule was listed for all druggists to follow in dispensing prescriptions.

The higher priced antibiotics are dispensed on a mark-up of between 30% to 40%. The reasons for the above mark-up are varied. Some follow the manufacturers suggested price list, other follow competitor's prices, still others follow the everlasting fear of arousing the customer's ire by so-called overcharging.

The reasons why most prescriptions departments are not profitable and self-supporting are first; too few prescriptions, and second, too low pricing of prescriptions.

It's time we woke up and stopped living in a dream world. Two plus two does not add up to ten. Let us face the following facts:—The average drug store is open 14 hours a day. The average hourly rate for a pharmacist is $ 2 and up. By simple arithmetic, we arrive at a total of $ 28 and up for a pharmacist working 14 hours a day. The average store would be happy to average 20 prescriptions daily. Continuing our arithmetic problem, we find that each prescription must show a net profit of $ 1.40 to pay the pharmacist for his days work.

This does not coincide with the average price of an average prescription of about $ 1.25, not including the high priced antibiotics of course.

Unless the pricing structure is changed, the prescription department will not be profitable if the average prescription filled, total about 20 prescriptions daily.

If the pharmacist were capable of filling 50 prescriptions daily, the profit picture would change for the better and your problems would then be solved. Your answer seems to lie with the doctor. Have him triple his prescription writing and Eureka!

Sincerely,
(Sgd.) Abram Schapiro

**Editor's Note from 1953:**

More prescriptions means greater investment and more over-head to take care of the increased volume. Nothing takes the place of adequate mark-up and professional fee for filling prescriptions.

# *Therapeutically Speaking...*

Pluronic Lecithin Organogel
A Novel Transdermal Vehicle for Drug Delivery

Jared Shayka PharmD
Cherokee Layson-Wolf PharmD, CGP

*The purpose of this article is to give the reader a brief history of pluronic lecithin organogel (PLO), discuss its use in pharmacy practice, describe how PLO is prepared including the process by which it is made and the purpose of each component. The article will also discuss medications that are being compounded in PLO, several studies evaluating its use as a viable drug delivery option and how to education a patient on its use.*

*The History of Pluronic Lecithin Organogel (PLO)*
For years, the scientific community has been looking for another transdermal option that was more versatile than the patch, could penetrate the layers of the skin, and enter the systemic circulation. In the early 1990s, Marty Jones and colleague Lawson Kloesel were experimenting with a variety of combinations of lecithin and isopropyl palmitate in various proportions, but could not get the correct consistency and physical characteristics.[1-2] After reviewing the literature, Jones came across an article discussing the use of Pluronic F-127 gel. They tried working with Pluronic F-127, but had difficulty getting it into solution. It was not until a cold January night in 1992 that Kloesel left the experimental pluronic gel in his briefcase and woke up next morning to find that it went into solution. After discovering that Pluronic F-127 was thermoreversible (e.g. solid at room temperature and liquid at cold temperatures), they were able to create a more stable preparation.[2]

*The Use of PLO*
PLO is a novel transdermal vehicle, which interacts with the outer skin layer (stratum corneum) and allows the drug to pass through the lipid layers and into systemic circulation.[2] Compounding pharmacists can use PLO to prepare medications that can allows for drug delivery for patients who have difficulty taking medications through conventional means. Those likely to benefit from PLO are animal, pediatric, elderly and hospice populations because of the difficulty with swallowing medications and variations in hepatic function that limit the use of certain medications. In addition, there is potential for increased side effects from medications given orally compared to those administered transdermally. [2-3]

*Preparation*
PLO is made up of two phases: aqueous (pluronic) and oil (lecithin) that are prepared separately. When preparing the pluronic components, ice cold water is first added, then agitated continuously, and placed in the refrigerator overnight to complete dissolution. The lecithin component is made by adding isopropyl myristate/isopropyl palmitate to lecithin and letting it stand overnight at room temperature to allow for complete dissolution. A preservative, such as 0.2% w/w potassium sorbate or 0.2-0.3% w/w sorbic acid, is added to both the pluronic and lecithin components. Upon completion of both phases, a drug is mixed into either phase depending on the polarity of the drug. When adding a drug to the pluronic component, additional amounts of water may be added to facilitate getting the drug into solution. Additional amounts of propylene glycol or ethoxyl diglycol can assist the dissolution process for the lecithin component. A high shearing method such as Luer Lock syringes, electronic mortar and pestle or an ointment mill is used to mix the two phases together. This allows for the formation of micelles, or a bilayer of lipids and pluronic, that contains the drug. It is important to keep the pluronic component cold while mixing to help ensure it stays in the liquid form.

*Components of PLO*

The components needed to ensure the correct formation of stable PLO are detailed below in Table 1.[1,3]

Table 1: Components of PLO [3]

| Theoretical Components | Details |
|---|---|
| Pluronic F-127 | Emulsifying, wetting, and solubilizing agent<br>Solid at room temperature<br>Liquid at refrigerated temperatures |
| Soya Lecithin | Permeation enhancer<br>Dispersing, emulsifying and stabilizing agent |
| Water | Solubilizes and stabilizes Pluronic F-127 and polar drugs |
| Isopropyl palmitate/ Isopropyl myristate | Solubilizes lecithin<br>Solidifies at refrigerated temperatures |
| Sorbic acid/ potassium sorbate | Preservatives |
| Drugs | Particle size less than 500 Daltons<br>pH 4.2-5.6 (same as skin)<br>Partition Coefficient of 1-3<br>Non-Toxic, irritating to skin<br>Not metabolized in skin |

*Drugs Prepared in PLO*

There are a variety of drugs being compounded in PLO and some examples are listed below in Table 2.

Table 2: Drugs Prepared in PLO[1,3]
(List is not all inclusive)

| Drug Class | Examples |
|---|---|
| Anesthetics | Benzocaine, lidocaine |
| Anti-emetics | Metoclopramide, ondansetron, promethazine, scopolamine |
| Anti-psychotics | Haloperidol, prochlorperazine |
| Calcium channel blockers | Diltiazem, nifedipine |
| Hormones | Estriol, estradiol, progesterone, testosterone |
| NSAIDs/Corticosteroids | Diclofenac, ketoprofen, piroxicam, dexamethasone |
| Opioids | Buprenorphine, methadone, morphine |
| SSRIs | Fluoxetine, paroxetine |
| Miscellaneous Medications by Indication | |
| Autism | Secretin |
| Hyperthyroidism | Methimazole |
| Parkinson's | Levodopa, selegiline |
| Combination Products/Use | |
| ABHR gel/nausea and vomiting | Ativan (lorazepam), Benadryl (diphenhydramine), Haldol (haloperidol), Reglan (metoclopramide) |
| ABK gel/Chemotherapy induced neuropathy | Amitriptyline, baclofen, ketamine |

*PLO in the Literature*

The major controversy surrounding PLO use is whether the drug in the PLO actually enters into systemic circulation. Unfortunately, literature available to support or negate these claims is limited. Available reports evaluate PLO use in humans by testing the compounded preparation's bioavailability after administering a single dose of a drug in PLO

and also effectiveness for repeated use, but not for extended periods of time. To date, there are not any commercial PLO products on the market. The following studies described assess either the bioavailability or effectiveness of several PLO products.

Ketoprofen 20% gel was tested in a small sample of healthy volunteers in which they received a single topical dose of 200mg. Volunteers were instructed to apply the gel to their inner wrist. The results of the study showed that the bioavailability of the ketoprofen 20% gel was 0.48% and the authors concluded that systemic effects were unlikely at this level.[4]

Promethazine gel was evaluated in 15 healthy volunteers who received 50mg of a single topical dose. The promethazine gel was applied to each volunteer's inner wrist. The absolute bioavailability of the topical preparation was 2%, but at least 50% of volunteers experienced side effects such as sedation and drowsiness. The authors suggested further research should be conducted regarding bioavailability and antiemetic effects.[5]

ABHR gel (lorazepam, diphenhydramine, haloperidol, metoclopramide) was evaluated in a retrospective analysis with other antiemetics in hospice patients with either colorectal, pancreatic, or lung cancer. ABHR gel was selected for treating 15-18% of the total population of 584 patients with symptoms of nausea and vomiting. ABHR gel use resulted in a statistically significant reduction in the nausea and vomiting score from a median of 5 out of 10 prior to treatment and 1 out of 10 after treatment $p < 0.001$. The authors concluded that ABHR gel has equivalent efficacy to other antiemetic therapies in hospice patients that can be used to treat nausea and vomiting. They also encouraged future research to evaluate adverse effects of ABHR.[6]

*Patient Education*

When preparing and dispensing a PLO gel product to one of your patients, discuss with the patient the following counseling points listed on Table 3 to ensure safe and proper use of the product.

Table 3: Patient Counseling Points/ Clinical Pearls [2,7]

| |
|---|
| Apply to thigh, wrist, or back (Not hands or soles) |
| Let site dry and do not wash site for several hours after application to prevent removal of medication |
| If applying gel to another, wear gloves and wash hands after application to prevent absorption through your skin |
| Expect a warm and cool sensation after application |
| Should NOT be used if allergic to egg whites, soy, or active drug within gel |
| Rotate sites to decrease irritation |
| Do NOT apply to eyes, mouth, or other mucous membranes |
| Store at room temperature unless noted otherwise |
| Dispose of the gel by the date listed on the container |

*Conclusions*

Since the discovery of PLO gel as a transdermal vehicle, it has been used for a variety of medications to help deliver medications to treat patients that cannot take medications through conventional means. Although the PLO vehicle was developed over 15 years ago, more studies are still being conducted to determine if it is an effective delivery system. Randomized, controlled trials are needed that evaluate PLO drug preparations safety and efficacy over longer periods of time.

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Volume XXVI, No. 5

# Fibromyalgia:
## A Veritable Disease with Real Symptoms

*Thomas A. Gossel, R.Ph., Ph.D., Professor Emeritus, Ohio Northern University, Ada, Ohio and*
*J. Richard Wuest, R.Ph., PharmD, Professor Emeritus, University of Cincinnati, Cincinnati, Ohio*

**Goal.** The goal of this lesson is to discuss fibromyalgia with reference to how it is managed.

**Objectives.** At the conclusion of this lesson, successful participants should be able to:

1. identify the demographics and prevalence of fibromyalgia in the United States;
2. recognize the principles of fibromyalgia, including pathophysiology, clinical manifestations, and diagnosis; and
3. select from a list specific nonpharmacologic and pharmacologic management of fibromyalgia.

Long believed by some to be little more than a vague description of another, albeit unknown symptom complex, fibromyalgia is described today as a veritable disease with real symptoms! It is an idiopathic, chronic, common and complex musculoskeletal pain syndrome characterized by widespread soft tissue pain and tenderness in the absence of tissue damage. Affecting 3 to 5 percent of the population in industrialized nations, fibromyalgia is prevalent in 3.4 percent of women and 0.5 percent of men in the United States. Rheumatologists report that it is the second most common disorder, after osteoarthritis, both in its primary form and as an accompaniment of other rheumatic disorders. The disease accounts for 5 percent of patients in general medical practice, which results in a significant burden



Gossel



Wuest

on the nation's health system, as well as lost employment time and medical costs that are about three times higher than expenditures for people without fibromyalgia.

### Pathophysiology

The pathophysiology of fibromyalgia remains elusive. A genetic predisposition is suggested since it is more prominent in females and in some families. Specific trigger factors include physical trauma (especially of the axial skeleton [cervical, thoracic and lumbar spine]), surgical interventions, infections (by *Borrelia burgdorferi*, Parvovirus, Coxsackievirus, hepatitis C and human immunodeficiency virus), and acute or chronic emotional stress.

Emerging evidence strongly supports the notion that fibromyalgia is a disorder of central pain processing. Dysregulation of the hypothalamic-pituitary-adrenal axis and altered activity of serotonin, norepinephrine, substance P, and other neurohormones have been implicated in the transmission of painful stimuli that may contribute to heightened pain sensitivity.

This theory lends support to targeted central nervous system therapies, such as antidepressants and cognitive behavior strategies, which act through modifying the pain response. The concept of altered central pain processing helps explain why analgesics, whose activity is primarily mediated peripherally (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs]), are less effective unless a coexisting inflammatory disorder is also being treated. It is, therefore, essential to identify comorbid (concurrent but unrelated) disorders early and treat them appropriately. More research is needed to determine the pathophysiology of fibromyalgia, and therapies that will address the specific pain pathways involved.

### Clinical Manifestations

Patients report a considerable impact on their quality of life, and their perceived disability level is influenced by their mental health condition. Effective pain relief in these patients significantly increases quality of life.

Many symptoms of fibromyalgia overlap considerably with those of other chronic illnesses, such as chronic fatigue and irritable bowel syndromes, chronic migraine and tension headache syndromes, genitourinary afflictions, multiple chemical sensitivities and depression. Patients often complain of

**Table 1**
**ACR* Criteria for Classification of Fibromyalgia**

Widespread pain for at least three months, defined as the presence of all of the following:
- Pain on the right and left sides of the body
- Pain above and below the waist (including shoulder and buttock pain)
- Pain in the axial skeleton (cervical, thoracic or lumbar spine, or anterior chest)

Pain on palpation with a 4-kg force in 11 of the following 18 sites (nine bilateral sites, for a total of 18 sites):
- Occiput: at the insertions of one or more of the following muscles: trapezius, sternocleidomastoid, splenius capitus, semispinalis capitus
- Low cervical: at the anterior aspect of the interspaces between the transverse processes of C5-C7
- Trapezius: at the midpoint of the upper border
- Supraspinatus: above the scapular spine near the medial border
- Second rib: just lateral to the second costochondral junction
- Lateral epicondyle: 2 cm distal to the lateral epicondyle
- Gluteal: at the upper outer quadrant of the buttocks at the anterior edge of the gluteus maximus muscle
- Greater trochanter: posterior to the greater trochanteric prominence
- Knee: at the medial fat pad proximal to the joint line

*American College of Rheumatology

Adapted from: Millea PJ, Holloway. *Am Fam Physician*. 2000;62:1575-82, 87

widespread pain, poor sleep and fatigue. They may describe low back pain radiating into the buttocks and legs, as well as pain and tightness in the neck and across the upper posterior shoulders. Pain may be described as a burning or gnawing soreness, aching or stiffness.

Headaches are present in more than half of all persons with fibromyalgia. The prevalence of migraine in these individuals suggests a common pathogenesis. The proposed etiology of migraine has been characterized by a parallel dramatic failure of serotonergic systems, along with a defect in adrenergic transmission.

Many patients with fibromyalgia have an associated sleep disorder. During sleep, sufferers are constantly interrupted by bursts of awake-like brain activity, which limits time in deep sleep. They awaken frequently during the night, have difficulty returning to sleep, and feel exhausted upon awakening. Partly due to the poor sleep, patients describe their fatigue as overwhelming exhaustion.

Irritable bowel syndrome (IBS) is often present. A functional disorder of the gastrointestinal tract, affected individuals suffer from chronic abdominal pain and disturbed bowel function, without evidence of structural or laboratory abnormalities on routine testing.

A subjective swollen feeling in the joints without objective swelling, and paresthesia (numbness or tingling in the extremities) without objective neurologic findings are two important features of fibromyalgia. Stiffness that is present in the morning upon arising typically improves as the day progresses.

Patients often experience cognitive difficulties such as memory loss and difficulty expressing themselves in normal conversation. Other manifestations include anxiety, light-headedness and dizziness. Fibromyalgia patients also report dysmenorrhea, irritable bladder, vision irregularities, premenstrual syndrome, symptoms of Raynaud's phenomenon, restless leg syndrome and noncardiac chest pain. Symptoms are intensified by cold and humid weather, poor sleep, and physical or mental stress, and improved by warm and dry weather, moderate physical activity, adequate sleep and relaxation.

## Diagnosis of Fibromyalgia

While no currently available laboratory test can confirm the diagnosis of fibromyalgia, most patients describe a history of widespread pain with physical findings and the comorbid conditions described above. It is important to confirm the diagnosis of fibromyalgia by its own characteristics rather than as a result of exclusion from other pathologies.

Although the condition of fibromyalgia dates back to early 20th century, it was not until 1990 that the American College of Rheumatology (ACR) defined specific criteria for the classification of fibromyalgia. These criteria (Table 1) require the presence of chronic (≥3 months), widespread musculoskeletal pain in at least 11 tender points on testing at 18 specified sites. An important consideration of the physical examination for a positive diagnosis of fibromyalgia is to systematically palpate (press) on the skin at the 18 sites, applying a moderate and consistent degree of pressure using the thumb of the dominant hand. The amount of force applied should be such that the examiner's thumbnail is blanched. The pain must occur in all four quadrants of the body and the axial skeleton. The tender points are distinct, predictable anatomical sites that are normally more sensitive to pressure than the surrounding tissue. They differ from other painful trigger points in the body in that they are not sites of tissue damage, tightness or pathology. They do not produce spontaneous pain and are usually unknown to the patient. It is known that some patients who clearly suffer from the classic symptoms of fibromyalgia will respond affirmatively to fewer than 11 of these tender points. Men generally have a higher tenderness threshold and fewer men than women respond to a complete "set" of at least 11 positive tender points despite clearly having symptomatic disease. This may partially explain why more women than men receive the diagnosis of fibromyalgia. All this said, the ACR classification criteria for diagnosis of fibromyalgia provides a sensitivity and specificity of nearly 85 percent in differentiating fibromyalgia from other forms of chronic musculoskeletal pain.

Moreover, other symptoms of fibromyalgia including chronic fatigue, altered sleep patterns resulting in unrefreshing sleep, dizziness, emotional distress, postural hypotension and memory disturbance often fluctuate in intensity, and pain appears in different sites. Flares can be induced or worsened by situations such as emotional stress, physical exertion, concurrent illness or even seasonal changes.

## Management

Obtaining relief of pain in fibromyalgia can be a challenge. Support from family, friends, and the healthcare system is often lacking. Optimal management includes nonpharmacologic and pharmacologic measures. The American Pain Society Fibromyalgia Panel recommends a multidisciplinary approach (Table 2).

It is imperative that patients have input in the management of their disease. This can reduce anxiety and depression.

### Nonpharmacologic Measures

**Patient Education.** Although a major segment of patient education is received in the physician's office, the effectiveness of organized programs in providing information, facilitating behavior change and improving symptoms is well documented. Providing helpful information directly or by steering patients to reliable sources of information affords great professional opportunities for pharmacists. Helpful information specific to fibromyalgia is available through the American College of Rheumatology (www.rheumatology.org), Arthritis Foundation (www.arthritis.org), Fibromyalgia Network (www.fmnetnews.com) and the National Fibromyalgia Association (www.fibrohope.org).

**Exercise.** The major goal for patients with fibromyalgia is to maintain normal function in everyday activities. An exercise program should include multiple dimensions that blend components of strength, aerobic (endurance) conditioning, flexibility and balance. To improve adherence to exercise programs, it is helpful to allow patients to choose the type of exercise (e.g., walking, bicycling, swimming, etc.) they prefer.

**Cognitive Behavior Strategies.** The major goal of cognitive and behavioral strategies is to help patients understand the effect that thoughts, beliefs and expectations have on their symptoms. Patients are taught to prioritize their time to achieve a comfortable balance between work, leisure and the activities of daily living.

### Pharmacologic Measures

Pharmacotherapy for fibromyalgia has been most successful with centrally-acting agents. Although the drugs are classified as antidepressants, muscle relaxants or anticonvulsants, they affect various neurochemicals (e.g., serotonin, norepinephrine, substance P) that have a broad range of activities in the brain and spinal cord, including actions on pain sensations and tolerance. Because symptoms of fibromyalgia wax and wane, effective treatment must be ongoing rather than episodic.

**Antidepressants.** Antidepressants have a long history in the treatment of chronic pain syndromes. There is evidence that they alleviate pain, and improve sleep quality and overall wellbeing in approximately one-third of fibromyalgia patients. Tricyclic antidepressants (TCAs), specifically amitriptyline (Elavil, etc.), are effective in providing analgesic effect, aiding sleep, and treating concomitant mood disorders. Selective serotonin reuptake inhibitors (SSRIs) in general have poor analgesic effect; however, fluoxetine (Prozac, etc.) has been shown to have a small but significant effect on symptoms in women with fibromyalgia. A TCA, SSRI or combination of both, produces mild to moderate

**Table 2**
**Treatment Measures for Fibromyalgia**

| Effectiveness | Pharmacologic | Nonpharmacologic |
|---|---|---|
| Strong evidence | amitriptyline<br>cyclobenzaprine | cardiovascular exercise, cognitive behavioral therapy, patient education, multidisciplinary therapy (*e.g., patient education and exercise*) |
| Moderate evidence | Dual-reuptake inhibitors (duloxetine, venlafaxine)<br>Fluoxetine, Pregabalin±<br>Tramadol with or without acetaminophen | acupuncture, balneotherapy*, biofeedback, hypnotherapy, strength training |
| Weak evidence | | chiropractic therapy, electrotherapy, manual and massage therapy, ultrasonography |
| No evidence | corticosteroids<br>melatonin, NSAIDs, Opioids≠,<br>thyroid hormone | flexibility exercise, tender (trigger) point injections |

*Balneotherapy = Treatment of disease by baths.
±Pregabalin (Lyrica) is now approved by FDA for treatment of fibromyalgia
≠An exception is made for tramadol, the synthetic codeine derivative, which has moderate evidence of effectiveness in fibromyalgia.

Adapted from: Goldenberg DL, Burckhardt C, Crofford L. *JAMA*. 2004;292:2388-2395

improvement in symptoms. One study showed that while 25 mg of amitriptyline or 20 mg of fluoxetine reduced symptom severity in fibromyalgia, the combination of the two drugs was twice as effective as either agent taken alone.

The newer serotonin-norepinephrine reuptake inhibitor duloxetine (Cymbalta) has shown promise in improving symptoms. Duloxetine 60 mg/day is effective in reducing pain and tenderness in patients with fibromyalgia regardless of whether patients have major depressive disorders. Venlafaxine (Effexor, etc.) has also been shown to be effective in alleviating pain and depressive symptoms in some small clinical trials, but this has not yet been corroborated by placebo-controlled, double-blind studies.

**Chronic Opioid Analgesic Therapy (COAT).** COAT may be suitable for treatment of mild to moderate pain or significant functional impairment, and for patients in whom other therapies are ineffective or contraindicated. Tramadol (Ultram, etc.), a centrally-acting, mild, narcotic analgesic, is somewhat effective in patients with mild to moderately severe pain. Combining tramadol with acetaminophen (Ultracet, etc.) has been shown to be effective without causing serious adverse effects. Other opioids have not been adequately tested in fibromyalgia; moreover, these patients seem especially sensitive to opioid side effects (nausea, constipation, itching and mental blurring), which often rules out the long-term use of these drugs.

**Other Analgesics.** Acetaminophen and NSAIDs are commonly used, but have no clear evidence of effectiveness. The skeletal muscle relaxant cyclobenzaprine (Flexeril, etc.) has been shown to be effective in improving sleep and decreasing pain.

**Pregabalin.** At the time of preparation of this lesson, pregabalin (Lyrica) is the first and only FDA-approved drug for management of fibromyalgia. When first marketed, the drug was approved for treatment of neuropathic pain associated with postherpetic neuralgia and diabetic peripheral neuropathy, and for adjunctive treatment of partial onset seizures in adults with epilepsy.

Pregabalin, which is structurally similar to gabapentin (Neurontin, etc.), is a derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). It does not bind directly to $GABA_A$ or $GABA_B$, or benzodiazepine receptors. It does not exert gabaminergic activity or block sodium channels, is not active at opiate receptors, and does not alter cyclooxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or norepinephrine reuptake.

Lyrica binds with high affinity to the $alpha_2$-delta site (a subunit of voltage-gated calcium channels) within the CNS. Although its mechanism of action remains unknown, there is evidence that binding to these sites may be involved in its action in fibromyalgia. *In vitro*, pregabalin reduces the calcium-dependent release of several neurotransmitters including substance P, possibly by modulation of calcium channel function. Its pharmacologic actions in fibromyalgia appear to be restricted to central neurons.

Adverse reactions range from mild to moderate in intensity with the most common ones (recorded at ≥5 percent and twice placebo) being blurred vision, dizziness, dry mouth, edema, weight gain and difficulty with concentration/attention. Because pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other drugs via metabolic interactions or protein binding displacement.

The recommended dose in treating fibromyalgia is 300 to 450 mg/day given in two or three divided doses. There is no evidence that doses of 600 mg/day confer additional benefit. Lyrica is taken orally with or without food. When discontinuing therapy, doses should be tapered down gradually over a minimum of one week.

Lyrica is a Schedule V substance. In clinical trials, abrupt or rapid discontinuation has led to symptoms including headache, diarrhea, insomnia and nausea, which are suggestive of physical dependence.

## Summary and Conclusions

The outlook for sufferers of fibromyalgia is better than ever before. The efforts of numerous individuals, support groups, organizations and medical professionals involved in helping people with fibromyalgia improve their quality of life are starting to pay dividends. Symptoms can fluctuate in severity, but the majority of patients do improve over time with proper treatment. With FDA approval of Lyrica, other, even more specific treatments may follow. By actively seeking the latest proven therapy, conversing with others who have fibromyalgia, reevaluating daily priorities, making appropriate lifestyle changes and working hard to maintain a hopeful attitude, the fibromyalgia sufferer can become the fibromyal-

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# Continuing Education Quiz

This month's questions are taken from the article on "Fibromyalgia: A Veritable Disease with Real Symptoms". Circle your answers to the following questions and mail the entire page to Maryland Pharmacist CE, 1800 Washington Blvd., Suite 333, Baltimore, MD 21230-1701. There is no charge for this quiz for MPhA members (non-members $10.00). The completed quiz for this issue must be received by 5/15/2011. A continuing education certificate for one and one-half contact hours (0.15 CEUs) will be mailed to you within six to eight weeks. Please type or print clearly.
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1. Fibromyalgia is more prominent in:
   a. males.
   b. females.

2. Fibromyalgia is considered to be a disorder of central pain processing due to altered activity of all of the following neurohrmones EXCEPT:
   a. acetylcholine. c. serotonin.
   a. norepinephrine. d. substance P.

3. The prevalence of migraine in patients with fibromyalgia is proposed to be due to a parallel dramatic failure of which of the following systems?
   a. Cholinergic c. Gabaminergic
   b. Dopaminergic d. Serotonergic

4. The term paresthesia is best described as:
   a. chronic abdominal and intestinal pain.
   b. difficulty expressing oneself to others.
   c. numbness or tingling in the extremities.
   d. sleepiness, lighheadedness, and dizziness.

5. The criteria for the classification of fibromyalgia requires testing for the presence of pain at which of the following number of specified sites?
   a. 3 c. 18
   b. 9 d. 27

6. Which of the following treatment measures for fibromyalgia has the strongest evidence of effectiveness?
   a. Amitriptyline
   b. Duloxetine
   c. Fluoxetine
   d. Venlafaxine

7. Nonpharmacologic treatment of fibromyalgia with balneotherpy involves use of:
   a. massage. c. exercise.
   b. hypnosis. d. baths.

8. All of the following should be components of exercise programs for patients with fibromyalgia EXCEPT:
   a. strength.
   b. jogging.
   c. balance.
   d. flexibility.

9. Which of the following opioids is considered to be somewhat effective for treating mild to moderate severe pain in patients with fibromyalgia?
   a. Hydrocodone c. Oxycodone
   b. Morphine d. Tramadol

10. Pregabalin (Lyrica) is a derivative of which of the following inhibitory transmitters?
   a. Acetylcholine
   b. Dopamine
   c. Gamma-aminobutyric acid
   d. Serotonin

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